Dynamics of Anterior and Posterior Limbic Contribution to Human Memory and Reality Monitoring – Functional Imaging Studies

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Valerie Treyer

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Promotionskomitee

Prof. Dr. Rodney Douglas (Vorsitz)

Prof. Dr. Alfred Buck (Leitung der Dissertation)

Prof. Dr. Armin Schnider

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Abstract

For rational actions it is important to recognize currently relevant information, i.e. to monitor ongoing reality. Patients failing to suppress currently irrelevant memory traces produce spontaneous confabulations (for review see Schnider 2003). Past information or habits gain access to their thinking and acting in the "now" instead of currently relevant information. To segregate irrelevant from relevant associations a filter function is needed. Such a filter indeed exists, as clinical studies on spontaneous confabulations (Schnider et al., 1996a) and a recent evoked potential study revealed (Schnider et al. 2002). The lesions of these patients always involve anterior limbic structures, particular the orbitofrontal cortex (OFC) or its connections to the basal forebrain, the anteriomedial hypothalamus, or the genu of the right internal capsule (for review see Schnider 2003).

The goal of this thesis was to reveal the underlying brain structures relevant for monitoring - or filtering - function in healthy subjects. To measure the brain's functional activation we used $H_2{}^{15}O$ positron emission tomography. With this method we are able to assure reliably cerebral blood flow as we have shown in several methodological studies (Carroll et al., 2002; Treyer et al., 2003; Weber et al., 2004). Cerebral blood flow is a parameter closely related to synaptic activations of the underlying neural circuitry (Mathiesen et al., 2000; Logothetis et al., 2001).

In a first study we used in healthy subjects a memory task that spontaneously confabulating patients cannot perform correctly. This task provokes a selection of currently relevant memory content. With this task we demonstrated that the left medial posterior OFC is activated during this filtering process whereas memory related structures in the posterior limbic system were only activated while subjects had to distinguish between novel and familiar stimuli. In a further experiment we could reveal an involvement of subcortical structures in this process. This was the first time the relevance of this orbitofrontal–subcortical loop in a memory task could be shown.

In a second experiment we tested if this activation of the OFC due to the task is changed when subjects had to respond to new pictures (defined as first appearance in a defined time window), but not to repetitions of pictures. The different instruction did not modulate the activity in the anterior limbic system as Elliott and Dolan (1999) described, but did show different activation in motor–control related regions. Therefore a behavioral inhibition, when a subject must not press a button while detecting a repetition, does not primarily rely on OFC functions.

In a third study we examined, if this filtering process is also activated when information was presented acoustically instead of visually. The results were virtually identical to our previous results using visual stimulation.

In a fourth study we revealed the importance of the baseline task position on apparent activation of memory critical structures as the anterior and posterior limbic system.

In a fifth experiment we examined the differences in the functions of the posterior limbic system while processing pictures, which deviate either in content from the learned picture, or in position. We demonstrated that these memory–relevant structures of the left brain hemisphere are involved particularly in the detection of deviant contents, and those in the right brain hemisphere particularly processed deviant positions. Furthermore, we demonstrated the involvement of the right OFC when obviously false information had to be ignored.

In conclusion, we demonstrate the role of the anterior limbic system as the vital brain structure for our ability to refer thinking to ongoing reality.

Zusammenfassung

Um der aktuellen Realität angepasste Handlungen ausführen zu können, ist es wichtig die aktuell relevanten Informationen zu erkennen. Es gibt Patienten, welche diese Fähigkeit verloren haben und basierend auf aktuell irrelevanten Gedächtnisinhalten spontane Konfabulationen generieren (eine Übersicht findet sich in Schnider 2003). Unangebrachte Gedächtnisinhalte und alte Verhaltensmuster gewinnen Zugang zu ihrem gegenwärtigen Denken und ihren aktuellen Handlungen. Eine Möglichkeit Relevantes von Irrelevantem schnell zu trennen bieten Filter. Solch eine schnelle Filterfunktion scheint tatsächlich zu existieren, wie klinische Studien (Schnider et al., 1996a) sowie eine Studie, die an gesunden Probanden evozierte Gehirnpotentiale untersuchte, zeigten (Schnider et al., 2002). Patienten mit spontanen Konfabulationen zeigen immer Läsionen im anterioren limbischen System, welches den orbitofrontale Kortex und subkortikale Strukturen beinhaltet.

Das Ziel dieser Dissertation war es, die für diese Filterfunktion relevanten Hirnstrukturen am gesunden Menschen darzustellen. Zur Messung der Hirnaktivität benutzten wir die Technik der Positronenemissionstomographie. Mit dieser Technik und mit radioaktivem Sauerstoffisotop markiertem Wasser sind wir in der Lage zerebralen Blutfluss, wie wir in verschiedenen methodischen Untersuchungen belegt haben, verlässlich zu messen. Relative Blutflussänderung ist ein Indikator für Änderungen der neuronalen Aktivität.

In einer ersten Studie untersuchten wir die Hirnaktivierungen in gesunden Probanden, während sie eine Wiedererkennungsaufgabe durchführen, deren Lösung insbesondere für spontan konfabulierende Patienten ein Problem darstellt, da sie eine Selektion relevanter Gedächtnisinhalte verlangt. Wir konnten zeigen, dass nebst dem orbitofrontalen Kortex auch subkortikale Strukturen involviert sind, wenn eine Unterscheidung von Relevantem und Irrelevantem verlangt wird. Des Weiteren konnten wir zeigen, dass das posteriore limbische System v.a. dann aktiv ist, wenn es gilt neue von bekannten Bildern zu unterscheiden.

In einem zweiten Experiment untersuchten wir inwiefern die anteriore limbische Aktivierung modifiziert wird, wenn die Probanden auf die Präsentation neuer Information aber nicht auf Wiederholungen reagieren müssen. Die unterschiedliche Instruktion bezüglich der Reaktion während der Wiedererkennungsaufgabe zeigte keine Modulation der anterioren limbischen Aktivierung, wie sie von anderen Autoren beschrieben worden war (Elliott and Dolan, 1999). Es zeigten sich dafür aber starke Differenzen in der Aktivierung von Gehirnzentren, die für die motorische Kontrolle zuständig sind.

Mit einer dritten Studie untersuchten wir, ob die gleichen Hirnregionen aktiviert sind, wenn wir in der gleichen Aufgabe anstatt visueller Reize akustische präsentieren. Das Resultat war vergleichbar mit dem der vorhergehenden Studien; der Filterprozess scheint nicht nur für visuell dargebotene Information zuständig zu sein, sondern auch für Informationen aus anderen Modalitäten.

In einer vierten Studie zeigten wir die Relevanz der Platzierung der Kontrollaufgaben innerhalb eines Gedächtnisexperimentes auf. Diese methodische Studie demonstrierte, dass aufgrund der zeitlichen Relation der Kontrollaufgabe zu einer Gedächtnisaufgabe eine scheinbare Aktivierung des limbischen Systems entstehen kann.

In einem fünften Experiment untersuchten wir die Unterschiede in der Funktion des posterioren limbischen Systems während es Bilder verarbeitet, die im Inhalt von Gelerntem abweichen, gegenüber solchen, die in ihrer Position abweichen. Wir zeigten auf, dass die gedächtnisrelevanten Strukturen der linken Gehirnhälfte v.a. für die Verarbeitung des Inhaltes zuständig sind, während diejenigen der rechten Gehirnhälfte die Position verarbeiten. Weiterhin konnten wir zeigen, dass der orbitofrontale Kortex aktiv wird, wenn offensichtlich veränderte aber dennoch irrelevante und zu ignorierende Information präsentiert wird.

Aus den Ergebnissen dieser Dissertation folgt, dass das anteriore limbische System eine zentrale Rolle spielt, unser Denken und unsere Handlungen auf die aktuelle Realität auszurichten.

Acknowledgment

I would like to thank my supervisors Armin Schnider and Alfred Buck, without both of them this work would not have been possible. I would also like to thank Prof. Gustav von Schulthess and the Clinic for Nuclear Medicine for the support and access to the imaging facilities. Furthermore, I would like to thank Rodney Douglas for the access to the inspiring atmosphere at the Institute of Neuroinformatics and for the support of my thesis. Special thanks also to my husband for his love and support.

Part I

Introduction

In the first section of this introduction I will give a short background of ongoing research in the field of memory function in humans. The modern memory research was shaped at the end of the 19th century on one hand by Ebbinghaus and his study of learning and forgetting, mainly reasoned during long promenades, and on the other hand by Ramon y Cajal, and his "neuron doctrine" of the last century, who – together with Sherrington and Eccles – laid the foundation for modern neuroscience. Since then, many theories about memory, learning and their biological background have been suggested. For this introduction, I will restrict myself on providing background material on the variety of classifications of memory function. I will focus on those functions that are relevant for the results presented in this thesis, namely functions of the mediotemporal lobe.

In the next section I will give a short anatomical overview of the anterior and posterior limbic system, since this thesis focuses on the dissociation of these two systems and their functions. Both systems will be introduced separately and only to a level of detail that is relevant for this thesis. With the technique used in this thesis only system level activation can be measured. Hence cellular mechanisms underlying memory functions in the respective brain regions are beyond the scope of this thesis and will not be discussed in the introduction.

In the focus of the studies during my PhD years there were the imaging techniques of positron emission tomography (PET) as well as functional magnet resonance imaging (fMRI). The cognitive studies of this thesis were all performed using PET, as this method provides at the moment the best information upon blood flow changes in the orbitofrontal cortex, which is one key region investigated in this thesis. Therefore only the PET technique will be explained in detail, both in introduction and discussion. The term "activation" of a certain brain region in human brains in quite all publications is used synonymously to an increase of cerebral blood flow (CBF) in $H_2{}^{15}O$ PET or blood oxygenation level depended contrast (BOLD) in fMRI. Even though both measures are coupled to neuronal activity, interferences from blood related measurements to underlying neuronal or better synaptic activity have to be taken with care (Mathiesen et al., 2000; Logothetis et al., 2001; Logothetis, 2002; Logothetis and Wandell, 2004), throughout this thesis, the term "activation" in the context of imaging studies will refer to blood flow changes, which are most of the time related to neuronal activity. In quite all imaging studies so called statistical parametric maps are presented, these maps show the T or Z values (the statistical parameters derived from a general linear model implemented in the program SPM (http://www.fil.ion.ucl.ac.uk/spm/)). The higher a value, the more statistically significant a difference is. Therefore higher values must

not denote also higher blood flow differences per se but at least higher consistency between and/or within subjects.

The methods section will only list methods that are common to more than one study of this thesis, while specific details to particular experiments are given directly in the respective chapters. Besides summarizing the PET technique, the statistical methods used for the experiments are generally described. The continuous recognition task, which is used in most of the experiments, will be described. Since it is more relevant for the choice of the methodology than for the main line of argument deployed in the thesis, the results of a first pilot study will also be described in the methods section.

The studies presented in part 3 of this thesis are divided into three chapters. In the first chapter I present the technical studies about blood flow measurements using PET. This presentation will be comparably brief, as we have already published most of the presented data (publication appended in appendix B). In the second chapter three studies are presented that use the same paradigm. In the last chapter two studies are presented which focus also on the dissociation of anterior and posterior limbic functions but using different paradigms. The studies in the second and third section are all presented with a short introduction to give a context for each study. Each study is discussed in the context of existing literature directly after its results have been presented. This partitioning allows me to conclude this thesis with a general discussion (part 4), which provides a more comprehensive summary of all studies described in the thesis and to provide a general outlook on future lines of research.

Chapter 1

Memory Classification

There are different ways to characterize learning and memory. Instead of giving a precise definition, a short description of different kinds of memory will be presented in the forthcoming paragraphs.
An old but still valid distinction is the one between short– and long–term memory. Already at the end of the 18th century Wiliam James has distinguished a primary from a secondary memory, the latter of which we today call long–term memory (James, 1890). Long–term memory can conceptually be partitioned into episodic and semantic memory. Alternatively, one may distinguish between implicit and explicit memory. Finally – in the context of the functional asymmetry of our two hemispheres – the distinction between verbal and non–verbal memory became important. In the following sections I select some of these memory concepts and discuss them shortly and in the context of functions of the hippocampal formation.

1.1 Short Term Memory

Waugh and Norman (1965) resume James' distinction between primary and secondary memory. They examined the primary memory with a so–called "probe–digit task". A series of digits was acoustically presented. The volunteer or patient had to memorize the digit presented after the declaration of the probe. At the end of the series the digit that represented the probe was presented. At this time the subject had to remember the digit presented before the probe. The earlier the probe was presented in the series, i.e. the further away from the disclosure it appeared, the more difficult it was to remember. To test if a time–dependent decay process was responsible for this loss in the primary memory, the experimenters presented the numbers at various speeds. No improvement showed up with increasing speed.

Therefore the authors conclude that old information stays just as long as it is not be overwritten by new one. This interpretation relies on the assumption of a fixed memory capacity. Atkinson and Shiffrin (1968) presented a "modal model of memory". This model follows the distinction between primary and secondary memory. However, they put a sensory buffer store in front of the short term memory. In this buffer information is processed in parallel. Sperling (1960) tested this so called iconic memory. During 50ms he presented volunteers a 3x4 field board, filled with randomly arranged letters. In one condition the volunteers were subsequently instructed to recall as many letters as possible. In another condition they had to recall only a single row, which was indicated by an acoustic signal. When the tone was presented within 500 ms observers could usually remember the complete row. When no tone was presented and the subject had to recall all items, they only remembered four to five letters. The fact that they could reproduce any row revealed that they had more information available than they could remember when asked for (Sperling, 1960). Hence the limiting factor for iconic memory is time: The iconic memory stores contents for about 500 ms, which is not sufficient to recall the entire list.

Information processed in the sensory buffer will be transferred into the next memory level. The control processes in the short term memory define which type of information is processed further. These control processes are: rehearsal, coding, decision and different retrieval strategies. They can be described as an attention process, which does not only focus on the external stimuli, but is also defined by goals, tasks and strategies of the subject. Input from the sensory register will be compared with existing knowledge from the long term store. Accordingly, information gets its associations and meanings.

The possible duration of storage in this system is difficult to measure, since information can be rehearsed. Rehearsal can extend this duration of storage until the information is stored in the long term memory. Without rehearsal the information disintegrates within 15 to 30 s. The capacity of this storage is limited to 7 ± 2 "units", where units can be numbers, words, sentences and even events or pictures (Miller, 1956). If words are presented for two seconds each, and you are asked to recall them afterwards freely, a further effect arises. Subjects recall the first and the last word of the list better than the others. These effects are called recency and primacy effect, respectively. The items mentioned at the beginning and at the end are more salient and therefore easier to remember than the items in the centre zone. In addition the primacy effect is related to the long term memory whereas the recency effect is related to short term memory. This can be shown by introducing a distraction that should "fill up" the short term memory: the recency effect disappears after 30 seconds (Glanzer

and Cunizt, 1966). The primacy effect can be strengthened on a small scale by enlarging the presentation duration of the items. These findings support that these two effects are implemented by different systems, i.e. the short– and the long–term memory. And indeed the primacy effect is decreased in amnesic patients (Baddeley and Warrington, 1970), whereas short term memory functions are not decreased in patients with mediotemporal lesions (Wicklegren, 1968). The short term memory functions seem to be mediated by the prefrontal cortex as shown in several imaging studies (D'Esposito et al., 1999; Postle et al., 1999). As this thesis is concerned with the memory functions of the mediotemporal lobe, short term memory will not be discussed any further in this introduction.

1.2 Long Term Memory

There are several ways to gain access to long term memory. On the one hand information has to be declared as "worthy" to be stored in the long term memory but information can also gain access directly from the sensory register. Thus Atkinson and Shiffrin (1968) also modelled phenomena of everyday life, such as how we can remember details later, although we were not conscious about them during the time of observation.
The long term storage also serves as knowledge base. Newly encoded information is compared with it and interpreted on this basis. It can occur that information at a certain time cannot be accessed. One can assume however, once consolidated, memory entries or engrams continue to exist as long as the physiological base remains intact. This is supported by the work of Ebbinghaus concerning time–savings for the relearning of senseless syllables. Even if something seems to be forgotten, i.e. is not consciously accessible, it exists in memory and can be reactivated by a repeated presentation (Ebbinghaus, 1992).

1.2.1 Episodic vs. Semantic Memory

The distinction of episodic versus semantic memory is strongly connected with the name of Endel Tulving. The episodic memory stores information on temporally dated episodes or events including temporal and local relations between these events and its organization is temporal. The semantic memory in contrast, resembles rather a mental thesaurus, incorporating the knowledge about words and other verbal symbols, their meanings, rules and algorithms, while information about time or modality of admission is not directly stored. Information can only gain access to the semantic memory, when it is understood. For infor-

mation to gain access to the episodic memory the perception is sufficient. Storage and recall of semantic information can operate automatically. In contrast, episodic memory must be recalled as a kind of mental re–experiencing of past events (Tulving, 1972, 1983a).
Tulving assumed two different systems underlying these two types of storage. It is difficult to study and test semantic memory exactly as not all humans share the same knowledge. Education as well as social background play an important role. Likewise one has to keep in mind, that semantic knowledge has its origins in experiences and events, and is thus not independent from episodic memory. Tulving also considered the possibility, that episodic memory is embedded as a subset within the semantic one (Tulving, 1984). This interpretation solves some of the problems a parallel existence of the two storages would cause.
In both types of memory information about the world is stored. The contents of both can be acquired by perception or mental contemplation. The content is accessible through introspection and can be communicated to others. Therefore these two categories are combined into the so–called declarative memory, in contrast to procedural memory. The content of the latter is not accessible by introspection, it cannot be communicated easily verbally but must be demonstrated over actions. Another distinction is the one between explicit and implicit memory. The former is combined with conscious awareness, while the latter is not. Episodic encoding is normally declared as explicit memory whereas priming as implicit memory. Even though this clear distinction of the different memory types is made, interactions between them can occur (Wagner et al., 2000).
But how is information processed in the memory system? Tulving himself gave an explanation on the system level in his "general abstract processing system" theory (Tulving, 1983b).

General Abstract Processing System (GAPS)

The so–called "general abstract processing system" is "general" as it considers all kinds of events and "abstract" as the components of this model are not further specified (Tulving, 1983b).
The elements of episodic memory can be divided into two processes, the encoding and the recovering ("retrieval") of information (upper and lower part of Figure 1.1). Both processes begin with perception (green outlined element Figure 1.1): in the first case the percept of information to learn, in the second case the cue for retrieval. In both cases a transformation follows as a next step (red outlined elements in Figure 1.1). On one hand the recoding of the encoded information in the memory and on the other hand the transformation of the so called ecphoric information to the remembered information. This kind of encoding has

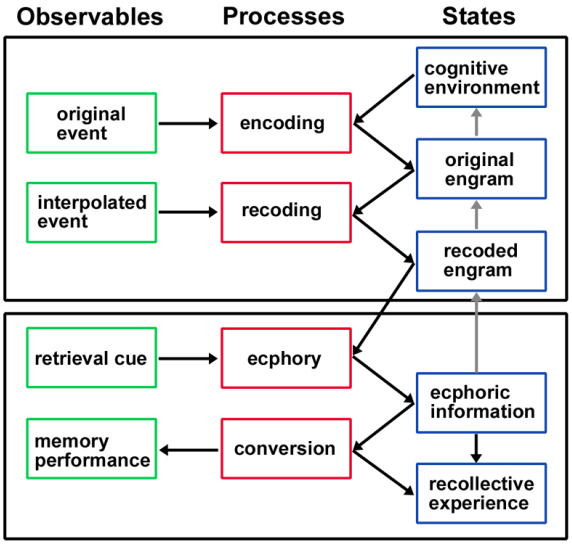

Figure 1.1: Schematic description of the "general abstract processing system" GAPS. Influence of one element on the other is visualized with arrows. The grey arrows reveal influences which are not relevant for the current memory act but for future ones.

a large influence on the later recall, called encoding specificity. The ecphoric information represents a combination of information from the currently presented cue and the stored memory. Therefore recall in this model is a constructional, synergetic act. It is important, that the system is in recall mode, to be ready to provide ecphoric information.

Encoding Specificity A phenomenon explaining this encoding specificity is diminished recognition. When subjects learned the pair A–B and had to recall B while A was presented they got 64% correct. But when the examiner presented B and asked if they had learned this word it was recognized correctly in only 24% of the cases (Tulving and Thomson, 1973). This is at a first glance a rather unusual result, considering that during recall the word must be remembered actively, while for recognition familiarity would suffice. These findings can be explained by encoding specificity. The pair of words was learned in a specific order. If B has to be recalled in the same context, i.e. together with A, it is easier to recognize than B alone. Several further experiments underline this and supported the theory of encoding specificity as the simplest explanation (Thomson and Tulving, 1970; Tulving and Thomson, 1971; Watkins and Tulving, 1975).

Recoding For Tulving encoding goes along with recoding, thus old engrams are updated due to new information. This is a strongly disputed aspect of his theory, as it states that the

old engram will be destroyed by this procedure. A behavioural study (Loftus, 1983) could show that healthy volunteers could not remember originally perceived information anymore. They first saw a road scene, in which a car drove past a priority signal. Afterwards they got the information that it over–drove a stop signal. The subjects believed to remember that the car over–drove a stop signal. Was the old engram really replaced by a new one or only supplemented by a more recent, probably easier accessible engram? A further experiment (Bekerian and Bowers, 1983), revealed a re–establishment of the old information, when the subjects were placed immediately before the recall into the original context. A similar result was shown by Christiaansen and Ochalek (1983). On the first day they presented a picture story. Subsequently, the subjects answered a multiple–choice test upon the story. Two days later they got a description of the story, which in three groups of subjects included four untrue statements. A fourth group served as control. Subsequently, all subjects had to estimate, how many details of the history they could recall. Afterwards one of the three deceived groups received the information that some details were wrong in the story. During the 45 minutes waiting period the subjects made personality tests and had word lists to learn. Before the final test a further group was informed that some details in the description were wrong. This group showed exactly the same performance as during the first test part directly after the slide session and as the control group. The deceived group, which did not receive a warning, made most errors. The group that was informed briefly after reading, showed better achievements, which were however worse than those of the control group. This study showed that subjects are able to gain access to the original information when informed about false information directly before they have to recall (Christiaansen and Ochalek, 1983).

Chapter 2

Anterior and Posterior Limbic System and their Functions in Humans

In this chapter I will introduce the two systems of interest for the work presented in this thesis. In the first part the most prominent and extensively studied structure of the posterior limbic system, the mediotemporal lobe with its key structure, the hippocampus, will be shortly described anatomically and functionally. In the second part some light will be shed on the anterior limbic structures and especially the orbitofrontal cortex. In this part I will also shortly present several positron emission tomography (PET) studies, which I performed during and shortly before my PhD and which are not included in the chapter describing the PET experiments of this thesis. This is on one hand the first PET study concerning the relation between anterior and posterior limbic system, which I performed as an undergraduate student. Furthermore, I will briefly present the data of our studies regarding anticipation of outcome, a function that also depends on the orbitofrontal cortex.

2.1 Mediotemporal Lobe

2.1.1 Anatomy

The mediotemporal lobe (Figure 2.1) as a part of the limbic system belongs to the allocortex, which forms a simpler laminated structure than the neocortex. The limbic part of the mediotemporal lobe consists of the hippocampus, the dentate gyrus, the subiculum, and the amygdala. Hippocampus, dentate gyrus and the subiculum together form the hippocampal

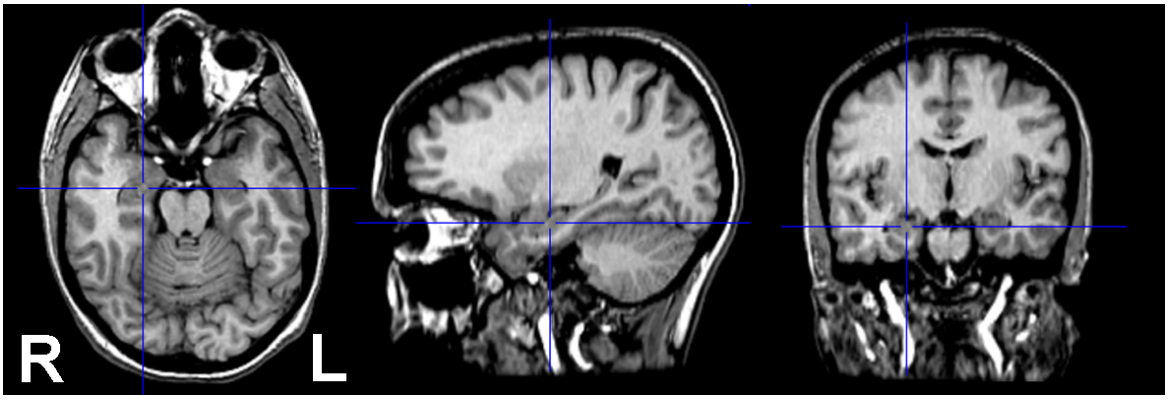

Figure 2.1: This is a transversal, sagittal and coronal view on the head of my hippocampal formation, scanned with a 3D MRI sequence.

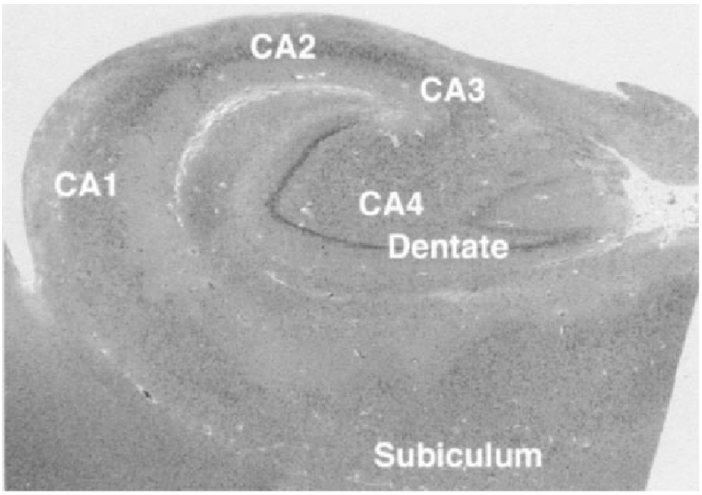

Figure 2.2: Coronal cut and nissl stain of a human hippocampus. From Kim, 2001.

formation. The formation is connected with the neocortical structures via the entorhinal cortex. The hippocampus proper is anatomically remarkable for its u–shaped structure on coronal cuts, which lead to the name ammons's horn (Cornus Ammonis). Its name is derived from a 3D reconstruction of this structure, which is reminiscent of the tail of a seahorse (lat. Hippocampus).

The hippocampus proper can be divided in four sub–regions: CA1 to CA4 (Figure 2.2). CA1 lies adjacent to the subiculum; CA3 and CA4 respectively form the end of the Hippocampus. CA2 is the less well– studied sub–region and it seems that the size shows a huge interindividual variability (Senitz, 1999). The dentate gyrus folds itself around the exposed end.

Connectivity

Within the hippocampal formation, projections from the dentate gyrus (granule cells; mossy fibres) project via the CA3 (pyramidal cells; Schaffer collaterals) region to the CA1 into the subiculum. The subiculum projects into the entorhinal cortex, which projects back into the dentate granule cells and connects the hippocampal region with the perirhinal and parahippocampal cortex. These structures are connected with unimodal and polymodal association areas in the frontal, temporal and parietal lobes (Rolls, 2000; Squire et al., 2004) (Figure 2.3). Perirhinal and parahippocampal cortices provide also the main neocortical input to the entorhinal cortex. The entorhinal cortex also receives other neocortical inputs directly from the superior temporal gyrus, insular cortex, the orbitofrontal cortex, the cingulate cortex and retrosplenial cortex. Beside this cortical–hippocampal loop the parahippocampal cortices have strong reciprocal connections, providing a basis for substantial information integration. Also inside the hippocampus a high level of integration is given due to several associational networks within and between the sub–regions (Lavenex and Amaral, 2000).
The amygdala is an almond shaped structure adjacent anterior to the hippocampus. It forms reciprocal connections with the regions CA1 and CA3, the subiculum, the entorhinal cortex, the thalamus and other diencephalic structures, the septum, as well as with a multiplicity of neocortical structures. Furthermore there are strong connections with different nuclei in the brain stem and midbrain (Amaral et al., 1992). The amygdala has clearly distinguishable nuclei. Each of these nuclei has specific projection areas. Due to the structure and the various connections the amygdala can be regarded as a central relay station of the limbic system.

The fornix, a bundle of axons, connects the hippocampus with the anterior part of the limbic brain, especially the septal nuclei and the mammillary bodies. The axons form an arch around the thalamus and do not proceed the direct path from the hippocampus to the anterior limbic system. The hippocampus projects also to the medial orbito frontal cortex, forming a hippocampo–prefrontal pathway as revealed in the rat. This pathway is also related to the circuits of the ventral striatum, especially the nucleus accumbens. This structure receives direct input from both, the prefrontal as well the hippocampal regions forming a circuit relevant for this thesis (Thierry et al., 2000).

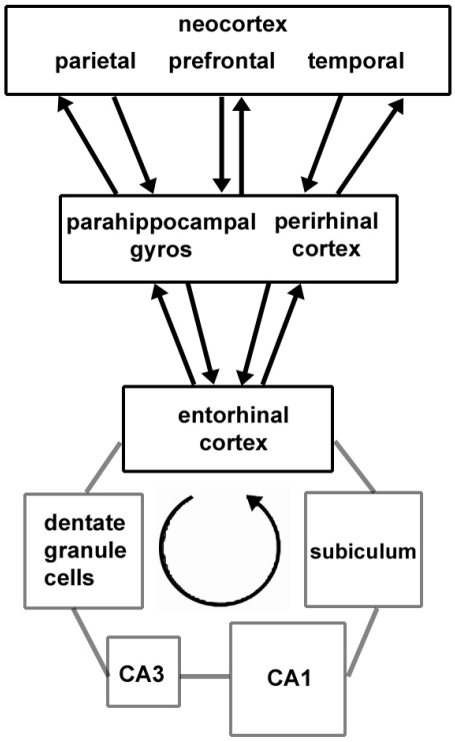

Figure 2.3: Schematic overview of the external connections, adapted from Rolls, 1999.

2.1.2 Mediotemporal Lobe and Episodic Memory – Experimental Studies

The so–called index theory assumes that information is not stored in the hippocampus (Teyler and DiScenna, 1986), but in the neocortex. The hippocampus accommodates only the map or the index of these neocortical regions. Therefore a reactivation of this information would express itself in a similar activation, as with the information acquisition. If the map is lost, it will be difficult to directly recall the knowledge. But old, generalized knowledge should nevertheless be accessible without such a map. Squire and Alvarez (1995) support a similar theory of the hippocampal contribution to memory, as far as its role is time limited. Others interpret the role of the hippocampus as a permanent one, insofar that for retrieval of episodic and spatial information the hippocampal system is always necessary (Nadel and Moscovitch, 1997). O'Reilly and Rudy (2000) clearly distinguish the fast continuous encoding process in the hippocampus from the slow cortical memory consolidation, which goes along with the findings on easily induced LTP/LTD in hippocampus and challenges induction in neocortex (Trepel and Racine, 1998).

The relevance of the hippocampal system for memory function as revealed in clinical studies and by imaging in healthy subjects will be discussed in the next paragraph.

Amnesia or the Lack of Memory

A patient is said to have amnesia if strong memory deficits exist without deficits in other cognitive functions. There are generally two kinds of amnesia, the anterograde and the retrograde type. Anterograde amnesia concerns learning of novel information and can be tested with the help of free recall or the recognition of learned word or figure lists. The short term recall of few items is hardly disturbed in amnesia (Vargha–Khadem et al., 1997). It is thus possible for the patients to keep information present for several seconds. A long–term storage is not possible. Patients suffering from amnesia after a hippocampal lesion usually suffer from anterograde and temporally limited retrograde amnesia. If occurring at all, the latter is usually limited to a few years before the disease onset, which is e.g. shown in the classical case studies of H.M. (Scoville and Milner, 1957) and R.B. (Zola–Morgan et al., 1986). Retrograde amnesia represents the actual loss of memory upon episodes stored before the disease. It is difficult to test old memories, as it requires knowledge on what the patient once had learned. Commonly this function is tested with autobiographic questions or general knowledge questions. The role of the hippocampus for such retrograde memory has remained unclear (Reed and Squire, 1998; Cipolotti et al., 2001). Several studies in rats, where controlled lesions can be made, observed a temporally graded retrograde amnesia, i.e. memory established closer to the surgery is more likely to be lost. This implies that the stored memory becomes independent from hippocampal functions after several (about 10 to 30) days (Winocur et al., 2001; Clark et al., 2002).

Case Studies

H.M. The most influential case in the history of amnesia is patient H.M. (Scoville and Milner, 1957; Milner et al., 1968). This was the first well–documented incidence of memory loss related to a hippocampal lesion. The patient suffered from heavy epileptic seizures. Since no pharmaceutical therapy provided satisfactory improvement, as a last therapeutical resort he underwent a bilateral medio–temporal resection. Both amygdalae and the anterior two thirds of the hippocampi were resected. A recent MR scan revealed bilateral symmetrical lesions, which covered the largest part of the amygdalae and entorhinal cortices. The perirhinal cortex as well as parahippocampal gyri were to a large extent intact. The caudal parts (aprox. 2–4 cm) of the hippocampi were intact but atrophic. Of interest is also an atrophy in the cerebellum and reduction in size of the mammillary bodies (Corkin et al., 1997).

Since his surgery H.M. suffers from severe anterograde amnesia. He does not remember what happened after his surgery. However, he can remember information up to 15 minutes if he is not disturbed. In addition his intelligence and his language performance did not worsen. A small retrograde amnesia was also documented. It goes back a few years prior to the surgery, so that he cannot remember e.g. the death of his uncle. Nevertheless, skill learning, such as a mirror–drawing task, does not seem to be impaired (Corkin, 1968). Taken together, the areas lesioned in H.M. thus seem to be most relevant for the induction of long–term episodic memory.

Since H.M.'s surgery no large bilateral resection was undertaken as therapy of pharmaco–resistant epilepsy. Nowadays the mediotemporal or amygdalahippocampectomy resection is limited to one hemisphere. This patient population again brought new insights into hemispheric specialisation and memory functions (Helmstaedter et al., 1994; Helmstaedter and Elger, 1996; Henke and Wieser, 1996).

Amnesia onset during Childhood Vargha–Khadem et al. (1997) provide clearer evidence on the role of the hippocampus for episodic in contrast to semantic memory. They studied 3 patients suffering from global anterograde amnesia, which had resulted from bilateral damage to the hippocampus at birth in one case and at ages 4 and 9 respectively in the other cases. All 3 patients were nevertheless able to attend school and to acquire semantic knowledge. Immediately following the learning epoch, all 3 could reproduce learned items – be it verbal or figural, to a normal extent. When asked 90 minutes afterwards, they could hardly remember any item. In daily life, they could not remember, where they placed objects, they were disoriented in time and had to be repeatedly reminded of appointments. Neither could they remember their activities of the same day. Despite these difficulties they could acquire speech, learn to read and write as well as comprehend their reading. One possible interpretation of these achievements is that perirhinal and entorhinal cortex, which are intact in these patients, suffice to acquire context–free knowledge, but fail to do so for context–based information, such as episodic knowledge.

This could also explain the disturbance in the acquisition of both episodic and semantic knowledge in patients H.M. (Scoville and Milner, 1957), E.P. and G.T. (Reed and Squire, 1998), in which those brain areas had also been removed. The few cases with well–defined hippocampal lesions, such as A.B. and L.J. (Reed and Squire, 1998), who also exhibit reduced anterograde semantic knowledge, are then especially striking in this context. Since in these cases a post–mortem analysis has not been available yet and neither is there any

high–resolution anatomical scan of A.B., effects on adjacent areas cannot be excluded.
Tasks involving feature–based associations or classifications show higher activation of the inferior frontal gyrus (Thompson–Schill et al., 1997). They confirmed the results of this fMRI study, studying patients with lesions to the inferior frontal gyrus, whose performance was especially reduced with respect to class–selection (Thompson–Schill et al., 1998). During the classification task the fMRI study revealed additional activation of the posterior temporal lobe, but no increased activation was found in the hippocampus (Thompson–Schill et al., 1997). This activation seems to be particularly associated with the recall of semantic information as such. This is also shown in Hodges et al. (1992), who presented five cases of semantic dementia. In all cases there was a lesion in the neocortical area of the left temporal lobe, but not in the hippocampal formation. For the semantic memory the hippocampal formation does not seem to be essential, at least not for the permanent storage of semantic information.

Separate Input and Output Regions of the Hippocampal Formation

With respect to episodic memory an fMRI study showed posterior hippocampus activation, resulting from successfully encoded visually presented words, in contrast to non–successfully recalled words (Fernandez et al., 1998). Another fMRI study showed differential activation for an encoding as compared to a recognition task (Gabrieli et al., 1997). Prior to the actual experiments, subjects had to memorize line–drawings. During scanning they were presented names of animals and objects and had to recognize which of those corresponded to the drawings. In five of six subjects, there was increased activation in the subiculum areas of the anterior temporal lobe, when names corresponding to memorized drawings were presented. This was also true for two subjects, who were presented drawings corresponding to previously learnt names. The encoding task required the subjects to judge complex scenes with respect to inside– vs. outside views. Some of the images were repeated during the session. When comparing those scenes presented once to those presented repeatedly, five out of six subjects showed a posterior activation of the temporal lobe in the area of the parahippocampus. The two subjects, who had to classify line–drawings into animals vs. inanimate objects, also showed the same activation pattern.
Being the main input region of the hippocampal formation, it is not surprising that the parahippocampus is more strongly activated when it comes to the encoding of novel as compared to previously seen information. Neither is the lack of significant hippocampal activation surprising, since learning takes place in either case. The recognition task shows

activation of the subiculum, which receives input from the hippocampus. One likely reason for the lack of significant differences in hippocampal activation between novel and learnt names is the fact, that either condition requires recognition, since the novelty of a name also needs to be recognized in the course of learning. The activity in the subiculum is thus likely to reflect the positive output signal that indicates a match.

Associative Encoding

The study of Henke et al. (1997) showed, that the hippocampus is mainly involved in associative learning in contrast to the learning of singular pieces of information. They presented pictures of unknown faces simultaneously with indoor or outdoor views of houses. Associative encoding of both items was achieved by asking subjects whether the person on the picture lives in the respective house or is just a visitor. During memorization of the items subjects had to indicate the gender and whether they were looking at an in– or outdoor view. Subjects thus encoded the items independently from each other. The comparison of these two conditions reveals increased rCBF in the right hippocampus and parahippocampus during associative learning. Hippocampus has also shown to be active for encoding pairs of abstract words (Henke et al., 1999). The hippocampus therefore seems to be strongly involved in establishing new associations, and thus for the integration of novel information.

Explicit vs. Implicit Memory

Another distinction between types of memory discussed in association with the hippocampal system is the one between explicit and implicit memory. Explicit memory tests have a prior conscious experience in common. Subjects know that they have to encode information and to later recall or recognize it. Unlike explicit memory, implicit memory cannot be accessed consciously. A typical implicit test, besides skill learning and habituation is priming – a prior experience improves performance without explicit memory for this experience.
Whether or not both types of memory processing are functions of the hippocampus, is strongly debated. Both camps presented intriguing theories and results against (Graf et al., 1984; Schacter and Graf, 1986; Moscovitch, 1992) and in favour of an involvement of the hippocampus (Chun and Phelps, 1999). At least an interaction of both forms can occur even when both types of memory are processed in different systems (Wagner et al., 2000). Animal experiments encounter the difficulty of missing language capabilities when testing implicit cognitive memory and have to deal with procedural implicit tests, i.e. motor learning. In two recent fMRI experiments we could show that the hippocampus is involved

in the establishment of associations of non–explicit, unconsciously presented information (Henke et al., 2003a; Henke et al., 2003c).

Lateralized Memory Functions

Our brain consists of two hemispheres, which are not perfectly identical. The advantage of the left hemisphere in speech processing has already been known since Broca (1861, 1863). Consequently, the linguistic abilities of the left hemisphere were examined more exactly (Benson, 1985). But later on it turned out that the right hemisphere also processes language to some degree. However, the language abilities of the right hemisphere are complex and can vary substantially across individuals (Zaidel, 1985).

Functional asymmetry is not found in all humans to the same extent, some even show right–sided language dominance. This does not always come together with a right–sided motor–dominance (i.e. left–handedness). There are about 61–70% left–handed persons with "normal" left–sided language dominance. Right–handed persons show in about 95–99% "normal" left–sided language dominance (Bryden, 1987; Hellige, 1990).

This dichotomy between the hemispheres is transferred to the memory functions and usually called material-specificity (Zaidel, 1985). Memory contents, which are verbalized or easy to verbalize, are processed therefore in the hippocampus of the left hemisphere. Difficult to verbalize information such as geometric, abstract figures and complex contents are processed more prominently in the right hippocampus (Henke et al., 1999). Left sided hippocampus resections result therefore in a reduction of the verbal memory abilities (considering a left–sided language dominance) (Sass et al., 1995; Helmstaedter and Elger, 1996; Regard et al., 1996). The function of the left mediotemporal lobe is well established as a processor of verbal information. The functions of the right hippocampus are usually more difficult to measure. Only after large right–sided anterior temporal lobe resections a decrease of performance in figural memory tests (Jones–Gotman, 1986) and spatial memory tests (Abrahams et al., 1997; Whishaw et al., 1997) can be measured. But orienting in a new complex environment seems to need both hippocampi (Maguire et al., 1996; Teng and Squire, 1999), probably because orienting in a complex environment needs storage of new spatial structure in addition to landmarks. But even though left and right hippocampus serve different functions, a plastic reallocation of these functions can occur, especially in epileptic patients (Henke et al., 2003b).

2.2 Orbitofrontal Cortex

2.2.1 Anatomy

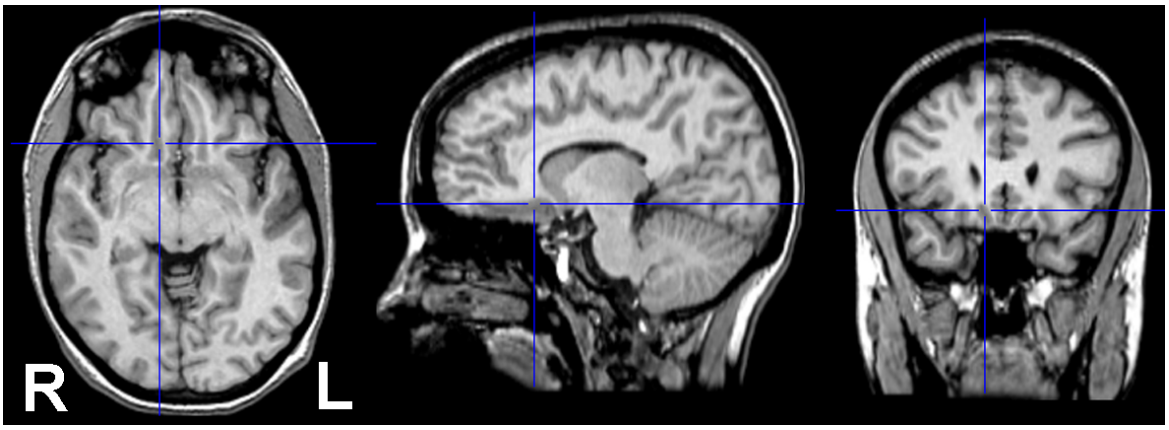

Figure 2.4: Transversal, sagittal and coronal view on my orbitofrontal cortex, scanned with a 3D magnet resonance imaging sequence.

The orbitofrontal cortex (OFC) is the most ventral part of the frontal cortex (Figure 2.4). In its dorsal vicinity there lies the prefrontal cortex and dorso–medially the anterior cingulum. Caudally to the OFC the limbic system is located.
Four almost parallel main sulci intersect the orbital surface into four gyri. The human OFC can be partioned on the basis of histological differences in different sub–regions or Brodman Areas (BA) (Figure 2.5): the frontal pole (BA 10), anterior orbital surface (BA11), lateral (BA 11) and medial (BA13) orbital surface, BA 14 on the ventromedial convexity, as well as BA 47 as the lateral parts of the orbitofrontal gyrus.

Connectivity

The OFC receives input from all sensory modalities: the olfactory, gustatory, somatosensory, visceral, auditory and visual regions (Rolls, 1996, 2004) (Figure 2.5c). Olfactory information is received directly from the olfactory bulb. The secondary (Iam, Iapm, BA 13) and tertiary (BA 11) olfactory cortices are located in the OFC. Area 13 and Ial compromise also the secondary gustatory cortex.
OFC receives input via the thalamus from the primary taste cortex in the anterior insular region. Visual information is received from the inferior temporal cortex, temporal pole and the anterior superior temporal sulcus in the area BA 47/12. Auditory information is projected from the superior temporal cortex into area BA 11 and BA 47/12. Somatosensory

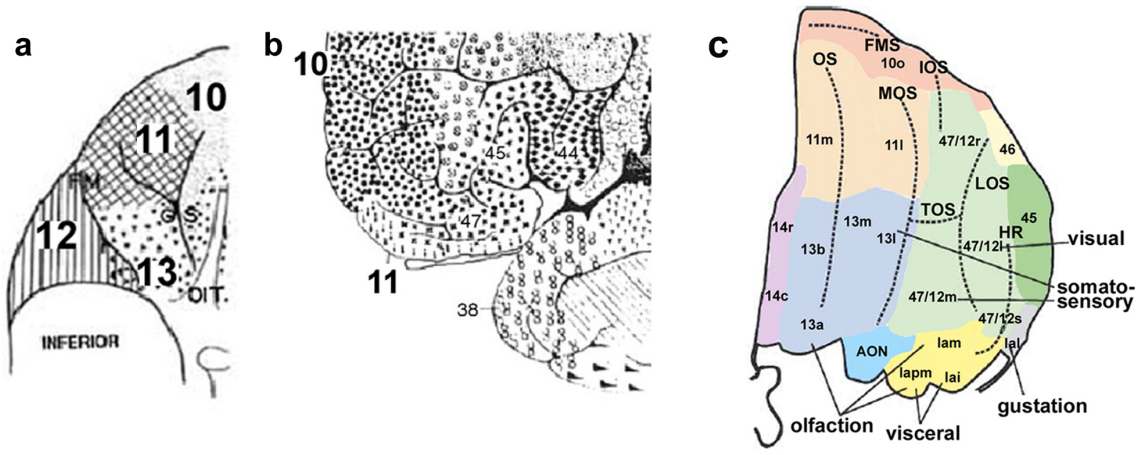

Figure 2.5: Different views of the Brodman Areas of the OFC: a) orbital surface b) lateral surface, adapted from Ongur and Price, 2000. c) Schematic overview of the sensory input areas in the OFC. The scheme depicts the orbital surface of the human OFC of the right hemisphere. Abbreviations used for Sulci: OS = olfactory sulcus; MOS = medial orbital sulcus; TOS = transverse orbital sulcus; LOS = lateral orbital sulcus, IOS = intermediate orbital sulcus; HR = horizontal ramus of the lateral sulcus. Abbreviation used for Areas: AON = anterior olfactory nucleus, Iai, Ial, Iam, Iapm = subdivisions of the agranular insular cortex, numbers depict Brodman Areas and their sub–regions, adapted from Kringelbach and Rolls (2004).

information from areas 2 and 1 as well as from the frontal, pericentral operculum and the insula is projected also to area BA 47/12. The caudal OFC (Ial, Iapm) receives input from the visceral system from the ventrolateral posteriomedial thalamic nucleus.

The reciprocal connections with the amygdala, the subiculum, the entorhinal and the perirhinal cortex link the OFC with the limbic emotion and memory system. The amygdala projects in high density to BA 13 and BA 47/12l but also to BA 10 and BA 14 (Figure 2.6). Some of the projections are topographically organised.

The OFC is also directly connected with the ventromedial striatum, the medial caudate and the ventral putamen. These connections form a striato–pallido–thalamo–cortical circuit (Ongur and Price, 2000). The ventral striato–pallidal circuit seems to take part in reward–guided choice behavior (Schultz et al., 1998). Besides the projection from the ventral pallidum to the medial mediodorsal nucleus of the thalamus and its reciprocal interconnection with the OFC the intralaminar nuclei form also extensive connections with the ventromedial striatum and the OFC. The efferent connections with the autonomic nervous system are established through the hypothalamus and the brainstem (the periaqueductal gray). These two regions receive also projections from the temporal lobe and the dysgranular insula. For this thesis a frontal–subcortical loop is of special interest: the dopaminergic modulation of

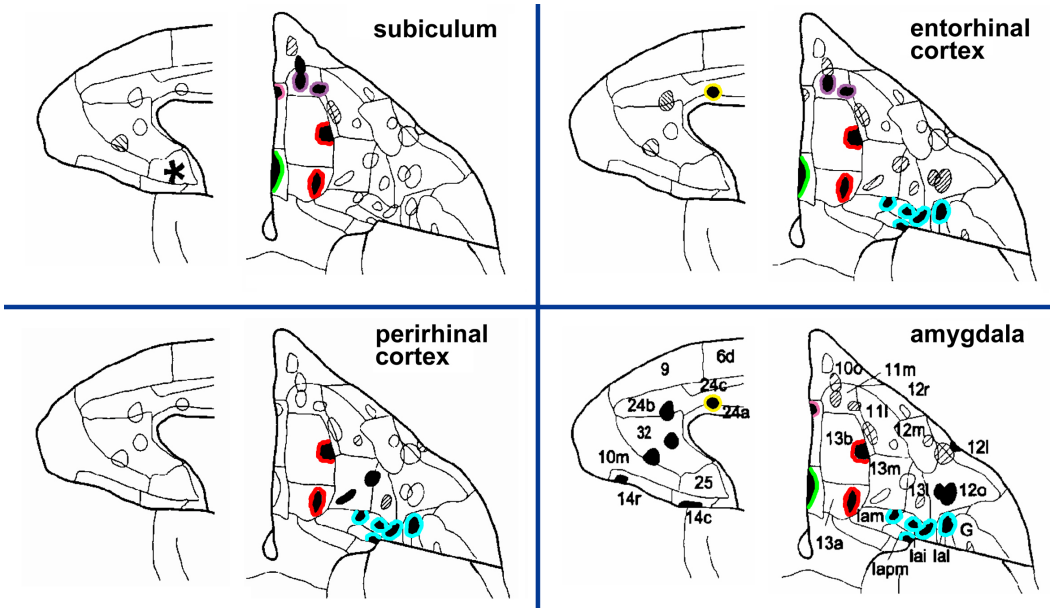

Figure 2.6: Schematic overview of the limbic input areas in the OFC. The scheme depicts the medial and orbital surface of monkey OFC. The outlined regions indicate the injection sides of retrograde axonal tracers. The black filled regions produced many labelled cells in the respective limbic region, hatched outlined regions produced only few. The coloured outlines are added to code for similarities between the projections. The red regions are connected with all four regions, whereas the green and cyan regions receive input from three origins. The lilac, rose and yellow outline depict regions with two common projection sides. (modified from Ongur and Price, 2000).

the OFC from the substantia nigra through the basal ganglia and the thalamus (Alexander et al., 1986; Augustine, 1996). These circuits are also connected to the hippocampal system via the hippocampo–prefrontal cortex pathway (Figure 2.7) (Thierry et al., 2000).

2.2.2 Functions – an Overview

The human orbitofrontal cortex (OFC) is involved in olfaction, taste, reward processing and social behavior (Anderson et al., 1999; Bechara et al., 2000a; Elliott et al., 2000; O'Doherty et al., 2001b). In a recent PET study we could also show that the OFC is involved in the processing of 5a–Androst–16–en–3–one (a boar pheromone) in male human subjects, even though the subjects did neither perceive an odour nor differentiate it from a pure air (manuscript in preparation for submission; an overview of the study is given in the appendix B).

The OFC is also linked to memory. Especially processing of novel information, i.e. encoding, seems to be also mediated by the OFC (Frey et al., 2000) and also to be independent of

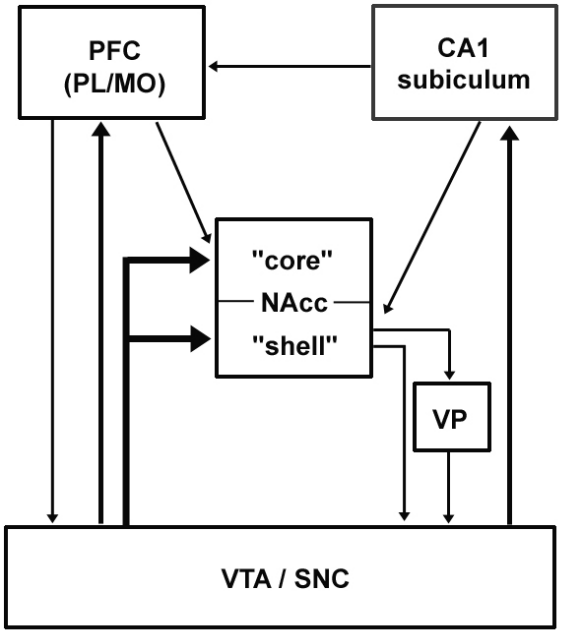

Figure 2.7: Schematic representation of the hippocampo–prefrontal cortex pathway with the nucleus accumbens, adapted from Thierry et al. (2000). PFC= preforntal cortex; PL/MO = prelimbic/medial orbital areas; VP = ventral pallidum; VTA = ventral tegmental area; SNC = substantia nigra pars compacta.

the emotional valence of the stimuli (Frey and Petrides, 2000, 2002). In these studies the right lateral posterior OFC was activated when subjects memorized a series of meaningless pictures. The OFC seemed to be more engaged when a deviation from expectancy occured, i.e. when the pattern differed from one that is typical in the context of the task (Petrides et al., 2002). Furthermore, the OFC is related to the distinction between true and false memories (Cabeza et al., 1997; Slotnick and Schacter, 2004) and the recall of temporal contextual cues (Fujii et al., 2002) as needed for source memory, bearing information of the location and time a memory trace was acquired.

From animal studies it is known that neurons in the OFC that are modulated by dopaminergic signalling, show reward related activity (Hikosaka and Watanabe, 2000). They are especially involved in reward discrimination (Schultz et al., 1998, 2000) (Figure 2.8). Reward or the reward–predicting signal do not just enhance learning through motivational factors, but also represents currently relevant information insofar as information leading to reward is relevant per se. But the OFC is only a part of the reward system. The neurons in the other parts of the dopamine modulated system show similar responses to reward related stimuli as the OFC (Schultz et al., 1997; Hollerman and Schultz, 1998; Schultz, 1999). These neurons are not just activated by the reward stimulus per se, but can also detect deviation

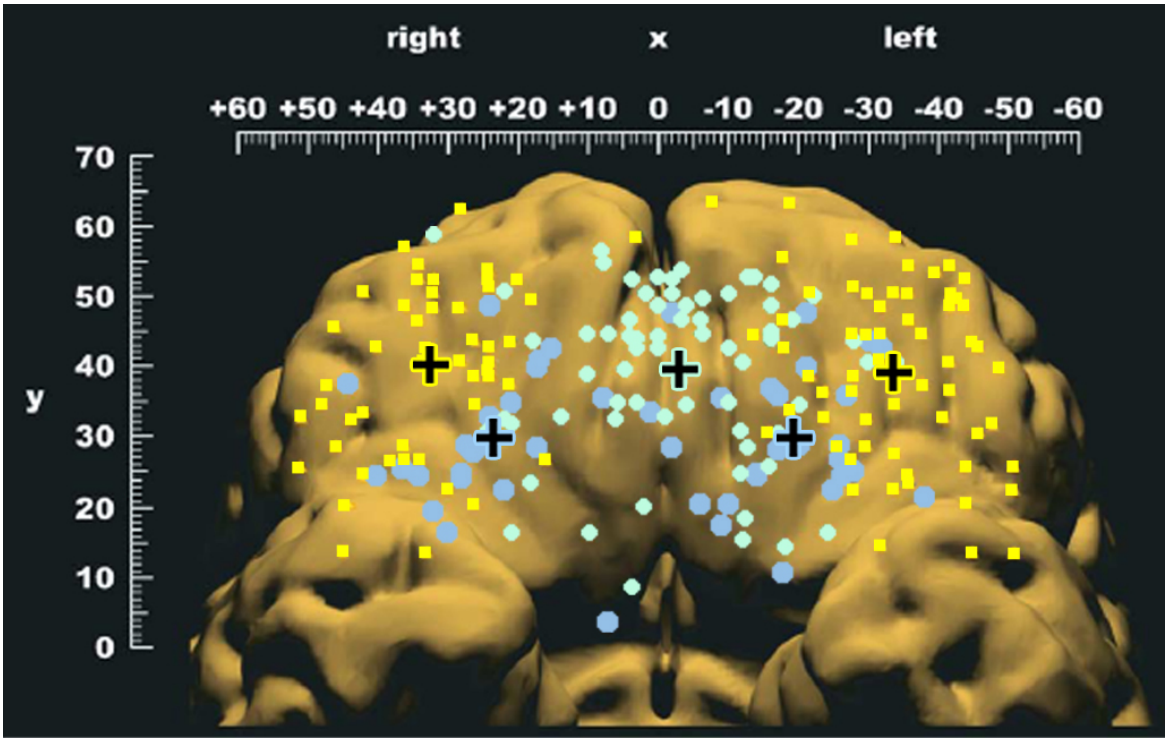

Figure 2.8: Results from a meta study Kringelbach and Rolls, 2004 displayed on the orbital surface of a rendered human OFC, modified for display purposes. The blue circles are placed on regions related to motivation–independent reinforcer representation. The centres of mass of the two clusters are located in the lateral OFC (blue cross). The green circles show regions related to monitoring the reward value. The centre of mass is found in the medial OFC. The yellow squares depicts region that are related to impending changes of behaviour. The centre of masses lied more lateral and anterior then the blue, reinforcer related activations.

of anticipated reward – may it be in time or strength. Neurons of the ventral striatum code e.g. expectations of predictable and reward related events and seem to be important for motivational control (Schultz et al., 1992).

In a recent PET study using a dopaminergic tracer (^{11}C–raclopride) it could be shown that dopamine is released in the human striatum during a reward related video game (Koepp et al., 1998). The OFC functions have been study excessively with so–called gambling tasks, where decision making, emotion and monetary reward play a major role (Bechara et al., 2000a). Patients with lesions in the ventromedial prefrontal cortex (OFC) fail in such tasks, as they are insensitive to the consequences of their actions, persisting even when aversive consequences have to be anticipated (Bechara et al., 2000b). The goal in gambling tasks is to maximize the gain. Nevertheless, their patients persistently drew cards from a high–risk deck, while healthy subjects as well as dorsolateral prefrontal lesion patients preferred cards from a low–risk deck, which resulted in higher winnings in the long run. Besides obvious gambling tasks, also a visual reversal–learning task, in which correct answers are rewarded

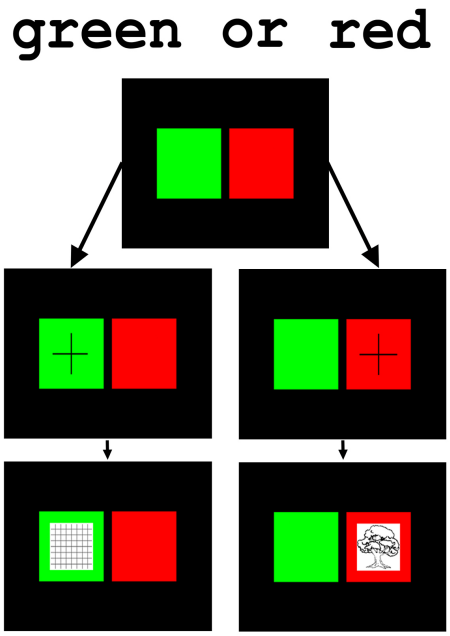

Figure 2.9: The subjects had to choose either the green or the red rectangle. After pressing the button a cross appeared on the chosen rectangle. After 1.5 sec the feedback appeared, in this case the picture appeared when the subject had chosen the red rectangle, the place–holder (grid) appeared when the green was chosen.

and false ones punished, activates the OFC in both cases (O'Doherty et al., 2001a). OFC is involved when feedback is given per se, irrespective of its valence (Elliott et al., 1997).
In a recent PET study using an easy anticipation paradigm we show that the OFC is also activated irrespective of whether or not explicit reward is provided (Figure 2.9) (Schnider et al., 2004). The following conditions were scanned:

- *AlwaysSame:* the object always appeared behind the same rectangle.
- *Change:* the object was absent on every 1^{st} to 4^{th} trial.

In these two conditions, subjects were asked to indicate the presumed position of the "object" based on the outcome of the previous trial, and to refrain from guessing.

- *Guess:* similar design as the *Change* condition, except that subjects were told that object position was random and that they should guess.
- *PlaceIt:* subjects asked to position the object themselves behind one of the rectangles.
- *Baseline:* object visible; subjects asked to indicate where the "object" was presented.
- *Reward:* In a further experiment the *Change* trial was performed using an explicit but not real–time displayed monetary reward for every correct choice (aggregate max. 30 CHF.).

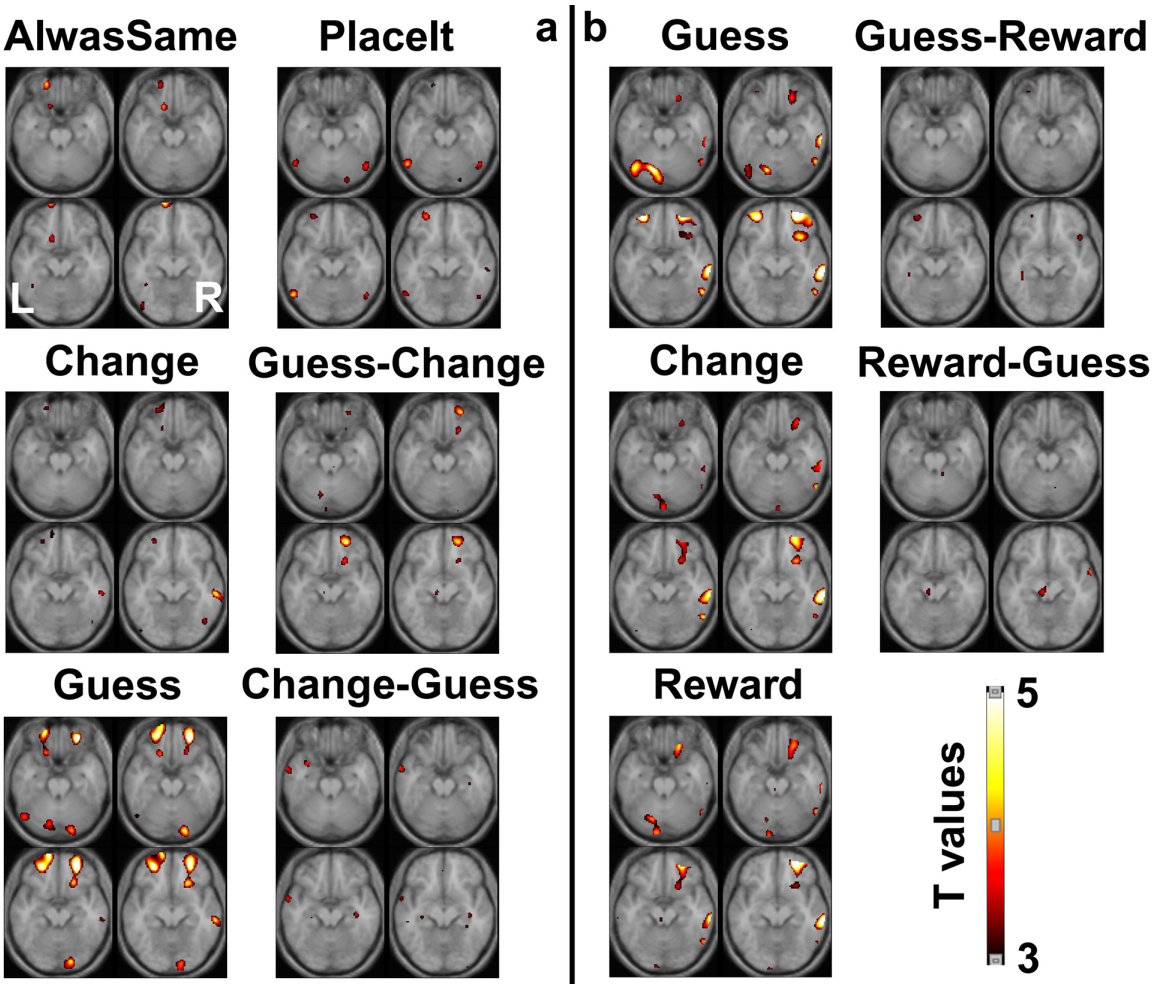

Figure 2.10: The statitistical maps are overlaid on a reference anatomy. a) Results of the first anticipation experiment, without an explicit reward related trial. The first column as well as the first picture in the second column shows the results of the baseline contrasts. The latter two pictures revealed the direct comparisons between the *Change* and the *Guess* condition. b) in this experiment only the *Guess*, *Change plus Reward*, *Change* as well as the baseline condition were performed. Again the first column shows the results of the baseline contrast, the second the direct comparisons.

Only the strength of the activation in the OFC varied over conditions, compared with the baseline (Figure 2.10). It was strongest during the guessing condition, where subjects knew that there is only a 50% probability to get a correct result. When an explicit reward was added during the *Reward* condition the activation of the OFC slightly increases but never as strongly as during the *Guess* condition. There are many possible reasons for the strong activations during guessing. The most important difference of this condition to the other ones is the interpretation of the feedback, which should not be related to one's action as the outcome is unpredictable. Does this mean, that the outcome is more emotionally interpreted than rationally and therefore activates the OFC to a higher degree? The relevance of the action for the outcome cannot be the relevant factor, as it is similar in the *PlaceIt* condition. Comparing the conditions *Guess* directly with *Change* revealed a higher mediotemporal activation during *Change*. This shows that the choice made before must be remembered to perform the task. During *Guess* a stronger right OFC activation was revealed than during *Change*. Since the outcome of the *Guess* condition is uncertain for the subjects, prediction cannot be based upon experience, they can only guess. Elliot et al. (1999) also supposed that the OFC activation they found in their guessing condition (guessing color(red/black) or suit (hearts,diamons,clubs or spades) of a playing card) compared to their "report" condition (card is seen face up) is related to uncertainty as the activation increases with the number of possibilities. This seems to activate the OFC in a strong manner.
In the last part of this chapter I will discuss to what extent the OFC is relevant for humans to perform rational actions and to select the currently relevant memory traces.

Specific Deficits after Lesions in the OFC – Spontaneous Confabulations

For rational actions it is important to recognize currently relevant information, i.e. to monitor ongoing reality. Patients failing to suppress currently irrelevant memory traces produce spontaneous confabulations (Van der Horst, 1932; Kopelman, 1987; DeLuca and Cicerone, 1991; Schnider et al., 1996a, b). Failures in suppressing a preferred response have already been shown after lateral frontal lesions and even stronger after OFC lesions in monkeys (Mishkin, 1964). Patients act in the present on the basis of information of the past, which is not relevant anymore or even true. That means, not just storage of new information is important, but also selection of currently relevant memories.

Spontaneous Confabulating Patients Spontaneously confabulating patients, as defined in several clinical studies, occasionally act on spontaneous and apparently invented

stories, which can be traced back to real events. They act on currently irrelevant memory traces, as if they were linked with the ongoing reality (quoted from Schnider, 2003):

- "A retired dentist, who had suffered rupture of an aneurysm of the anterior communicating artery, inadvertently left the hospital, was convinced that patients were waiting for him in his clinic."
- "Another patient, a 58–year–old women hospitalised following rupture of an anterior communicating artery aneurysm, was convinced that she was at home and had to feed her baby, although her 'baby' was over 30 years old at the time."
- "A tax accountant with extensive traumatic destruction of the orbitofrontal cortex left the hospital convinced he had a meeting with the county's financial director."

All of these patients are convinced of the trueness of their stories. They fail to adequately process information within the "now", they fail to monitor reality (Schnider, 2000).
The term "reality monitoring" used here is different to the one used in the context of false or illusionary memories (Johnson, 1991). It is not about monitoring the plausibility of remembered past events, but about deactivation of already activated memory traces, which are irrelevant for the present situation. In a natural environment this kind of deactivation is necessary to cope with the multitude of associations a complex stimulus can evoke. Without this deactivation or suppression, as it is called in this context, already activated information, which does not pertain to ongoing reality, remains active and induces inadequate behaviour. The ability to suppress enables humans to live in the present and to act according to the current situation. Without suppression a reasonable selection process in our environment full of distractions would be difficult. Comparing the spontaneously confabulating patients with patients suffering from severe amnesia, they did not differ on common measure of memory or executive functions. But the spontaneously confabulating patients failed to distinguish between currently relevant and currently irrelevant items in repeated runs of a continuous recognition task, caused by an inability to suppress previously presented but currently irrelevant (distracter) items (Schnider et al., 1996a; Schnider and Ptak, 1999). The recovery from spontaneous confabulations is accompanied by the recovery of this suppression capacity (Schnider et al., 2000b).
The lesions of these patients always involve anterior limbic structures, in particular the orbitofrontal cortex (OFC) or its connections in to the basal forebrain, the anteriomedial hypothalamus, or the genu of the right internal capsule (Schnider, 2003). The same task,

which these patients failed in, activated the medial posterior OFC in an $H_2{}^{15}O$ PET study with healthy volunteers (Schnider et al., 2000a).

Part II

Methods

Chapter 3

Positron Emission Tomography

3.1 Data Acquisition

All of the studies presented in this thesis are performed using $H_2{}^{15}O$ Positron emission tomography (PET) to measure relative cerebral blood flow (CBF). In our context, the alternative for brain–imaging in healthy subjects, functional magnetic resonance imaging (fMRI) is accompanied by several shortcomings and artefacts. Other alternatives such as magnetencephalography (MEG) and electroencephalography (EEG), were not feasible for the present interest, as both methods have poor spatial resolution. PET is a tool to measure virtually every physiological process – if an appropriate tracer is available.

3.1.1 The Radiopharmaceuticals

Radiopharmaceuticals for PET are substances, that are labelled with a neutron deficient and therefore unstable isotope, which tends to emit a positron (β^+–decay). The radionuclides are generated in the cyclotron, which in our case is located directly adjacent to the PET scanners.

To generate a β^+ emitter, lightweight nuclei (usually protons or deuterons) are brought to collision with heavy targets. In case of ^{15}O (max. positron energy 1.72MeV) this typically uses the reaction d + $^{14}N \rightarrow {}^{15}O$ + n, which is achieved by bombing natural N_2 gas (99.6% ^{14}N) with low energy deuterons. The ^{15}O nucleus is unstable and decays to the stable nitrogen isotope ^{15}N under emission of a positron and an electron–neutrino ($^{15}O \rightarrow {}^{15}N + e^+ + \nu_e$). The positron quickly annihilates with an electron of the tissue, which results in two photons, which travel 180° in opposing direction. Their energy is given by the rest masses

of electron and positron to 511keV each. The energy allows the photons to penetrate the body tissue. Consequently, the photons resulting from the β^+ decay are detectable by the PET scanner (see next section).

The positron emitting isotopes as typically used in PET have a half–life between minutes and hours: ^{18}F has 109.7 min, ^{11}C 20.4 min, ^{13}N 9.96 min and ^{15}O 2.04 min. The free length of path for a positron in tissue depends on its energy and thus on the emitter. For ^{15}O it is biggest with 1.05 mm (FWHM) and for ^{18}F with 0.22 mm (FWHM) the shortest. These results in a better resolution for ^{18}F compounds, as the distance between emission of the positron and annihilation is smallest. The radioactive isotopes have to be carefully selected as it would not make sense to combine a short living isotope with a slow binding substance. Therefore isotopes with long half–lifes are chosen to image slow physiological processes whereas fast processes– as for example blood flow, are preferable measured with short living isotopes, such as ^{15}O. This isotopes also have the advantage, that they enable several measurements in succession during one scanning session, as after 10 min virtually all ^{15}O has decayed and the next application can take place without misleading accumulation of prior applied substances.

There are many types of radiopharmaceuticals in use at the PET Centre in Zurich and many new compounds are developed together with the PSI and ETH. But for the data presented in this thesis only the $H_2{}^{15}O$ compound is of interest and will therefore exlucively be discussed.

3.1.2 The Scanner

Our scanner is the GE Advance PET scanner; therefore any device specific technical information refers, unless otherwise stated, to this specific scanner.

In order to detect the positron emitting isotope, the PET scanner measures the photons resulting from the aforementioned annihilation process. The scanner detects coincident photons, i.e. photons arriving within a time–window of 12ns. Since the two photons are emitted in an angle of 180 , the annihilation took place on the line, that connects the two points where the photons were measured, the so–called line of response (LOR).

At which point on the LOR the annihilation took place is unknown. Only from the many annihilations taking place along all LORs a reconstruction of the underlying distribution of the radioisotopes can be calculated.

Photon detection uses a bismuth germanate oxide (BGO) scintillation crystal. To enable a fast simultaneous detection of all LOR's in PET a whole ring of detectors is needed. The

individual detectors in PET are arranged in 18 detector rings with a diameter of 92.7 cm. Overall there are 12096 crystals, which are assembled 6x6 within a detector modules with a volume of 4x8.5x3 mm and combined with two photomultiplier tubes, which convert the UV light induced by the absorbed gamma–photon into an electronic signal, amplifies it and also stores information about the angle and energy. Each detector module is in coincidence with several others lying on a possible LOR. When one detector is activated by a photon the corresponding event is searched and recorded as a coincidence along their LOR. The event count within this respective LOR is increased.

There are two possible modes a PET scanner can run in, 2D and 3D. In the 2D mode retractable lead septa are placed between the detectors, which are retracted during 3D scanning. These results in less detected LOR's in 2D mode, as coincidences are only detected when the detector modules are not separated by the septa. Therefore cross plane incidences are neglected. These results in an overall of only 25% of the counts as measured with 3D mode, but reveals better resolution. In 3D mode the number of random and scattered coincidences increases and has to be corrected for. One major problem with 3D modes are the signals of both ends of the field of view (FOV). In these regions photons are emitted into the detectors from outside of the FOV, therefore increasing random and scatter coincidences. Some PET–Centres use a shield to prevent this decrease in signal to noise ratio, which is not available here.

During an emission scan the spatial distribution of the injected tracer is measured within the FOV and averaged over the duration of the scan. Such scans can be made close together using a dynamic acquisition protocol. One such scan is called a frame. After the acquisition the information is transferred and prepared for reconstruction. The raw data is stored as a matrix. It is formed by a two–dimensional array coding position and angle of all the acquired LOR's in all detector rings during the emission time.

To extract an image out of the LOR measurements during an emission scan (while an emitting objects lies in the scanner) a reconstruction is necessary including several corrections. One obvious and very important dimension to correct is attenuation. Photons emitted from within an organ are attenuated more strongly by the tissue as the probability of an interaction is higher than in air. Therefore it is less probable to measure the photon by the detectors as it will be scattered, losing energy and its direction. Knowing the density and thickness of the measured body part along the LOR's this attenuation can be corrected. Classically this is performed with a Germanium (^{68}Ge) transmission measurement. Two bars positioned in 180° made of ^{68}Ge are implemented in the scanner. During the transmission scan they cycle

around the FOV emitting a slight radiation at 511keV. The distribution along the LOR's reveals information about attenuation of the transmitted energy. This scan in the case of a brain study needs 10 minutes time. This can be shortened using a CT scan with a PET/CT scanner (Kamel et al., 2002). The transmission information has also to be corrected with a so–called blank scan. This scan is made the same way as the transmission scan but without any object in the FOV, therefore without attenuation of the transmitted photons. The resulting map codes information about the current sensitivities of the detectors. This scan is performed once a week to set the correction map and every day for quality control. A ratio of the transmission and the blank scan is used to correct the emission information for photon attenuation.

For the reconstruction of the data presented here, we used the classical filtered back–projection algorithms for 3D acquired data. This results in a 35 slice image with a transaxial field of view (FOV) of 55 cm, an axial FOV of 15.2 cm and a spatial resolution of 2.34x2.34x4.25 mm in a 128x128 matrix with a true resolution of 7 mm.

Further corrections had also to be applied to gain good quality. Especially the detector efficiency had to be monitored. Since the photo multiplier tubes have different and changing gains, these gain maps and a coincidence time alignment are updated and correction maps are computed once a week to ensure a uniform response.

Furthermore, the dead time of the system has to be taken into account. As the photo multiplier also stores energy information, events with too high energies when two photons arriving indiscriminable at quite the same time can be discarded. When the next photon arrives while the previous photon is processed it will not be measured. This is also the case when the input is too strong so that the system is saturated or "paralyzed". This happens when the applied dose per area is too high. Another important factor to adjust for, are random coincidences. They increase with the rate of single incidences on each detector. They bring a uniform background into the image, with a mean level of twice the coincidence window multiplied with the single rates. This decreases image contrast unnecessarily. The random correction can be estimated online, using a delayed coincidence window, so that during this time no true but just random "coincidences" are measured.

After all these corrections a value has to be attributed to each pixel. This value can be on a relative scale or expressed in kBq/ml when the scanner is well calibrated.

3.1.3 $H_2{}^{15}O$ Application

We use an automatic injection device for $H_2{}^{15}O$ application. The cyclotron produces continuously ^{15}O–O_2 which is directly delivered to the injector. To combine ^{15}O with the physiological and sterile H_2O saline solution a promoter is needed. ^{15}O–O_2 reacts continuously with H_2 over a palladium–alumina catalyst at a temperature of 200°C in a lead box underneath an infusion pump system and passes through a gas–liquid exchanger to gain the $H_2{}^{15}O$ solution. A radioactivity detector (Geiger–Müller probe) continuously measures the radioactivity of a volume corresponding to the application volume (8ml). At regular intervals a conversion factor is determined using a calibrated detector. As the cyclotron produces at a constant rate ^{15}O, the amount of injected radioactivity can be set prior to application to a certain level by simply adjusting the cyclotron current (approx. 3μA).

For most of the measurements we use the pump to apply a bolus injection, but for some patient studies we switched the injection device into a continuous injection mode with a rate of 60ml/h. The amount of applied radioactivity was controlled and the same as for a bolus injection study. This enabled us to perform event related PET.

The constant infusion technique for measuring cerebral blood flow using short lived isotopes has been known for quite some time. A summary of the theoretical background is given by Huang et al. (1979). The technique has not been widely used, because the necessary equipment such as a cyclotron to produce ^{15}O is only available in a few PET centres. At the PET centre in Zurich, a special custom–made infusion pump is used to produce and administer the $H_2{}^{15}O$ as a constant intravenous infusion. Most other groups used masks to deliver the $C^{15}O_2$ gas, which was then converted to $H_2{}^{15}O$ in the body. With such a mask system the level of the radioactivity in the body cannot be controlled as accurately as with an intravenous infusion. In Zurich, the technique is now routinely used to assess cerebral blood flow in patients evaluated for a revascularisation procedure.

For cognitive brain studies, the infusion technique has several advantages compared to the usually used bolus method. Cerebral blood flow is continuously monitored and not only at intervals, which are at least 10 minutes apart. This allows us assessing the whole time course of cerebral blood flow in response to a task. The technique is in this respect similar to the event related methodology developed in magnetic resonance imaging. In fact, the same methods are employed to analyse the data.

We use a dynamic protocol, which bins the acquired images in frames of freely defined duration. The images are reconstructed as normal 3D brain images but without decay correction

as due to the constant infusion which correct by itself for the decay.
For the clinical studies measuring CBF changes due to acetazolamide challenge we scanned up to fifty 1 min frames and for the cognitive studies two–hundred 10 to 15 second frames.

3.2 Statistical Evaluation of Cognitive rCBF Measurements

In this part I describe the global method used in all forthcoming studies. Details of different or additional methods are provided directly in the chapter the experiment is described in. The base is a standardized statistical package (SPM99) (Friston et al., 1995a; Friston et al., 1995b), which was originally developed for PET data analysis.

3.2.1 Statistical Parametric Mapping and Region of Interest Analysis

For each scan, 300–450 MBq $H_2{}^{15}O$ were administered as a slow bolus with a remotely controlled injection device. The amount depended on the numbers of scans and was calculated to not exceed an individual radiation dose of more then 4mSv. PET counts were recorded over 60 sec after the arrival of the bolus in the brain. A ten minute transmission scan was performed between the second and third set. Attenuation corrected data were reconstructed into 35 image planes (slice thickness: 4.25 mm; matrix: 128x128; pixelsize: 2.34 mm). The accumulated radioactivity counts over 60 sec were taken as measure for cerebral blood flow. Statistical parametric mapping was performed as follows. First, head movement between the scans was corrected using the least squares method implemented in SPM. Then, all images of each subject were summed and transformed into stereotaxic space [Montreal Neurological Institute coordinates (MNI) as provided by SPM99]. The normalization included linear transformations and deformations based on non–linear basis functions. The resulting transformation matrix was subsequently used to transform each individual scan. A proportional scaling was applied for global normalization to remove global effects. To ameliorate residual interindividual anatomical and functional differences after spatial normalization, the scans were smoothed with a gaussian filter of 15 mm FWHM. The difference between conditions was then evaluated voxel by voxel using a general linear model appropriate for the study design. Afterwards the T–contrasts (one–sided) of interest were calculated.
In all studies we accepted results with T values higher than 3 or $p < 0.001$ (uncorrected for multiple comparisons). We did not consider whole brain corrections for multiple comparisons as we have clear a priori regions defined by clinical studies. We also did not apply a correction for the a–priori defined region as such a manipulation would only pretend a

correction for multiple comparisons. Furthermore, the studies presented here form a framework supporting each other. A priori knowledge is taken from previous results and from patient studies, allowing us to accept results that are uncorrected for multiple comparisons. Region of interest analyses were performed with PMOD (medical image quantification and modeling software www.pmod.com) and SAS 8.0 (SAS Institute Inc., 2000). An anatomical magnetic resonance image (SPGR T1–weighted 0.94 x 0.94 x 1.5 mm) was acquired from eight subjects and coregistered and realigned to the subjects mean PET image so that the evaluated normalization matrix could be applied to the anatomical T1 image in parallel to the PET images. This average anatomy is used throughout all figures displaying the results of the SPM statistic.

Chapter 4

The Task

In the following I will present the task we used in several studies presented in this thesis.
The task, which segregates spontaneous confabulators from other amnestic patients, comprises several runs of a continuous recognition task (Schnider et al., 1996a). It is not a simple recognition task, which normally would be composed of a learning part and a recognition part, where the learned items have to be detected within a series of new ones. During a run of the continuous recognition task subjects had to detect repetitions continuously, i.e. the first incident of an item and its repetition are included in the same run. This results in a mixture of encoding, i.e. seeing a picture the first time during the run, and recognition, i.e. detecting repetitions.
The special difficulty of this task is that in all runs, the same pictures are displayed in different order as in the runs before. In the first run all stimuli are initially novel, so an item appearing familiar in the ongoing run could be assumed as a repetition, i.e. a target. The performance in the first run depends primarily on new learning. In the subsequent runs, all items are familiar, the subjects have now to distinguish between appearance in the present ("now") and in previous runs (the "past") and not anymore on familiarity. The implicit task therefore is to select relevant information, i.e. repetition in the current run, and concomitantly to suppress now irrelevant memories such as previous repetitions in past runs. Currently relevant information is defined by the previous appearance of a stimulus within the same run.

4.1 The Task in–depth

The continuous recognition task consists of three runs (Figure 4.1). For all runs the same instruction is given and the same rules have to be followed: press the button of your device

when a stimulus reappears within the current run. The repetitions occur in a continuous fashion, i.e. there is no distinction between an encoding phase and a recognition phase, both take place at the same time. Every stimulus has to be judged either as first occurrence or as a repetition during the current run. The important point in this task is that during the second and third run the same stimuli in a new randomization are used, consequently the subjects must discriminate current (and therefore valid) repetitions from occurrences in previous runs.

During the first run encoding of new stimuli as well as distinction of novel and familiar stimuli must be achieved. During the forthcoming runs all stimuli are familiar, the subjects have to select and react on only the repetitions of the current run and cannot anymore base their judgements on familiarity.

The baseline task was performed 8 minutes after the recognition task unless otherwise stated. The baseline task was designed in parallel to the continuous recognition task and consisted of three stimuli of the same type. The subjects had to perform a one–back task, they had to press a button when an immediate stimulus repetition occurred.

This task, which distinguishes spontaneous confabulating patients from other amnesic patients, should not be confused with a source memory task, which also can activate the OFC (Fujii et al., 2002). Even though it is important to discriminate between the current and previous runs, the underlying functions are different.

4.2 Results of a First PET Study

To justify the methodology described in the remainder of the methods, I briefly report data of our study published in 2000 (Schnider et al., 2000a).

The study described in this section aims at showing that the same task as used with patients activates the orbitofrontal cortex in healthy volunteers. Despite being a full study of its own, this result may also be taken as pilot study to the experiments reported in this thesis. The participating subjects performed 5 runs of a task akin to the aforementioned continuous recognition task. However, we could not use the very same version of the task as used in the clinical studies, because this design would be too easy for young healthy volunteers. We thus considerably shortened the time between the different runs of the task to 90 seconds. The pictures reappeared not more than twice and targets of a previous run could also be targets in the current run. Therefore knowledge of the previous run gave no clue for a possible anticipation of a target or a distracter. Subjects were prepared and sensitised that

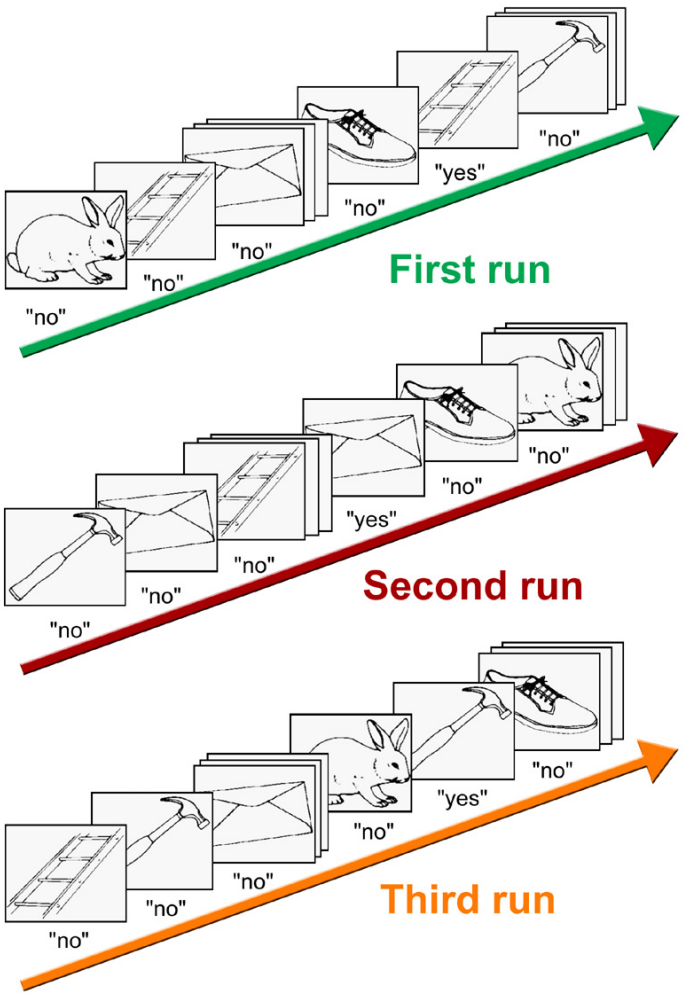

Figure 4.1: Continuous recognition task performed in several runs. In every run the same pictures are presented in different order. The patients have to decide if the saw a already the picture in the current run or if they saw it the first time in the current run.

picture repetitions in a previous run were irrelevant for the current run and that they should forget the previous runs and concentrate on the current run. These instructions should minimize the relevance of source memory and emphasize the relevance of the current run as an independent event.

The subjects saw in each run the same 60 coloured photographs (Corel picture library) and got the same instruction for all runs: to press one button on the device if a picture reappears in the current run, irrespective of occurrences in previous runs. Every picture was presented on the screen for 3 seconds with an inter–stimulus–interval of 1 second. In between each run was a 90 seconds break. The subjects performed in the scanner a preparatory run to familiarize with the task. This run included different pictures than the test runs. The baseline task included three new pictures, which were repeatedly presented. The subjects had to indicate immediate picture repetition, that means they had to compare the currently presented picture with the picture immediately seen before and decide if it is the same. This task is called "one–back task" as the test stimulus has to be compared with the stimulus seen before. In this version we used only three stimuli to minimize variations and memory load.

4.2.1 Brain Activation Due to New Learning

Comparing the first run with the baseline task revealed strong activation in the right hippocampal formation encompassing the hippocampus, parahippocampal and also and fusiform gyri (Figure 4.2A, h2). On the left side only the parahippocampal gyrus (Figure 4.2 A, h1) showed higher regional cerebral blood flow comparing to the baseline. Additionally a small area in the right rectal gyrus was also activated. A volume of interest (VOI) analysis revealed a decrease of activity in these clusters from run to run (repeated measures ANOVA; Figure 4.2D, h1: $F(2,7) = 3.9$, $p = 0.045$; h2: $F(2,7) = 7.5$, $p = 0.006$; gR: $F(2,7) = 21$, $p < 0.0001$).

4.2.2 Brain Activation Due to the Selection of Currently Relevant Memory Traces

The third and fifth runs revealed a different pattern. In these runs the task primarily required the subjects to distinguish between item repetitions within the present run and presentations in previous runs. In both runs the posterior medial OFC showed a significant

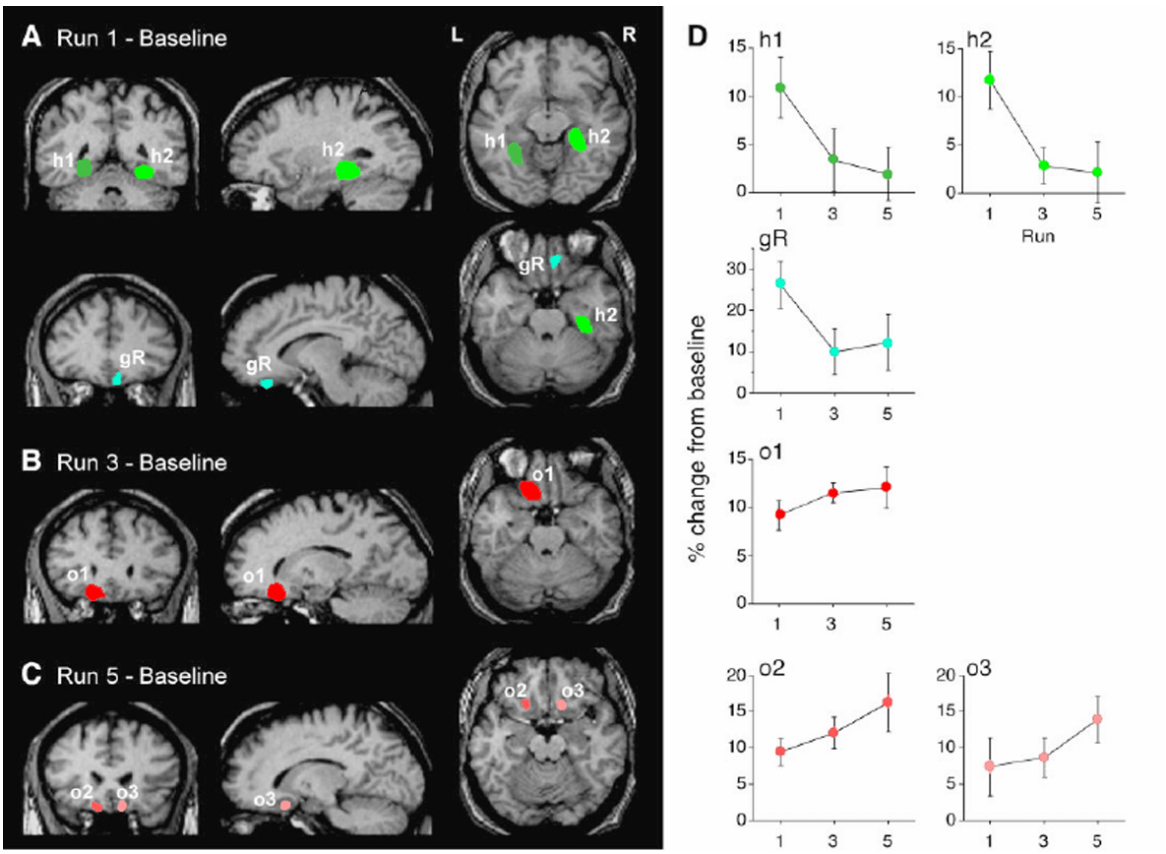

Figure 4.2: Results of the first PET study. The relevant activation are presented with a cut–off of $p < 0.01$ overlaid on a reference MRI. On the right side are the plots derived from the ROI analysis. (adapted from Schnider et al., 2000a)

activation compared to the baseline task. The activations were not completely overlapping in both contrasts. Comparing the third run with the baseline, revealed a large area of activation in the posterior portion of the left inferior frontal gyrus, lateral of the rectal gyrus (Figure 4.2B,o1), while in the fifth run compared to the baseline, this activation area was much smaller. A further activation was present in this contrast in the posterior medial OFC on both sides (Figure 4.2C, o2, o3). The VOI analysis showed that the activation increased non significantly ($p = 0.10$) in these regions from run to run (Figure 4.2D, o1, o2, o3). Nevertheless the interactions of h1, h2, and gR with o1, o2, and o3 with the run (1, 3, 5) were significant ($F(1,2) = 4.6$;p $p < 0.02$) in a pairwise repeated measures ANOVA.

4.2.3 Summary

This first study revealed an activation of the OFC while healthy subjects performed the task spontaneously confabulating patients failed in. Furthermore it revealed a dissociation of the anterior and posterior limbic system. The mediotemporal cortex was activated during the first run which mainly depend on new learning, whereas the left posterior medial OFC was activated during the third and fifth runs which both needed additionally a filter function to separate relevant and irrelevant repetitions.

Part III

Studies

Chapter 5

Methodological Studies

5.1 Different Methods to Measure Absolute CBF with $H_2{}^{15}O$

This paragraph will provide a short overview of the work on $H_2{}^{15}O$ measurements in PET we performed over the recent years. Even though this paragraph was modified for this thesis there is a high similarity to the text of published articles. The respective articles are provided in appendix B.

The uptake of $H_2{}^{15}O$ into tissue is related to blood supply. $H_2{}^{15}O$ is washed in (K1) and washed out (k2) within minutes. The time–activity curve (TAC) following an injection of $H_2{}^{15}O$ shows a relatively sharp peak in the arterial measurement and a delayed and dispersed curve in the tissue measurement. The peak is higher, the increase steeper and the washout faster, if the flow rate is higher.

One specialty of PET is that we can measure absolute values of physiological processes such as blood flow. This is a large advantage over MRI, where absolute measurements are not accurate (Carroll et al., 2002).

To measure cerebral blood flow (CBF) on an absolute scale, we need to know the input, which can be measured via continuous arterial sampling using an external sampling system. This is built like a little PET scanner incorporating two pairs of BGO crystals to measure coincidences of the arterial line. This procedure requires that an arterial catheter is placed in the radial artery of the subject. This provides information on the input into the brain. But as this measurement cannot be made closely to the brain but has to be performed at a distant place, the delay and shape differs from the true input curve in the brain. Feeding the arterial input and the tissue time–activity curve into a one–tissue compartment model then allows us to calculate absolute blood flow values.

5.1.1 A Method without a Need for an Arterial Catheter

This is a short summary of the paper Treyer et al. (2003b). The full article is appended in appendix B.

One major disadvantage of all models using real artery input information is the need for an artery catheter. Therefore we developed a method, which does not require arterial blood sampling. In contrast to the original method, quantification is derived from the washout parameter k2. This parameter depends on the shape rather than on the scale of the input curve. Therefore we can estimate an absolute flow without knowing the value of the actual inflow. The value of k2 represents CBF divided by the partition coefficient that is 0.85 in most of the cases. We compared the absolute values with Alpert's original method as gold standard and with Watabe's method in healthy subjects using a test–retest paradigm. Furthermore we showed that it is also a suitable method for the assessment of perfusion reserve using acetazolamide challenge [1] in clinical examinations.

5.2 Event–Related PET Using Constant Infusion Technique

As mentioned beforehand it is also possible at our site to infuse $H_2{}^{15}O$ at a constant rate. This enables us to perform CBF measurements over longer time scales. We performed several clinical studies using preoperative language activation or preoperative motor activation to determine the potential risk to lose a function after operation. Furthermore, this method seems to be suitable for the evaluation of epileptic activity, as we can correlate the measured time course with the seizure onset determined with a clinical EEG measured during PET scanning.

5.2.1 Estimating Cerebral Blood Flow Changes after Acetazolamide Injection

Since this study was published in Weber et al. (2004), only a short overview is given here. The original work is appended in appendix B. We used the constant–infusion technique to assess the baseline perfusion as well as the perfusion reserve after acetazolamide challenge in patients with cerebrovascular diseases. In normal subjects acetazolamide induces an increase of 30–40% in cerebral blood flow in grey matter. This increase is often called

[1] Acetazolamide is a carbonic anhydrase inhibitor. Carbonic anhydrase catalyzes the reversible reaction of the hydration of carbon dioxide and of the dehydration of carbonic acid. In response the CBF is increased to compensate for this.

perfusion reserve. If the perfusion reserve is diminished it indicates compromised perfusion. For a clinical assessment a baseline $H_2{}^{15}O$ scan before acetazolamide and a second scan after injection is needed. Furthermore the absolute cerebral blood flow for both scans has to be determined. One problem is to evaluate the best time point for imaging the perfusion reserve. The purpose of this study was therefore to continuously monitor cerebral blood flow to continuously measure the cerebral blood flow response.
The increase blood flow in non–pathologic areas started 1–2 min after acetazolamide injection showing the strongest increase from 0 to 10 min. In most of the patients, the clearest increase was found in the healthy regions. The pathological areas showed an initial decrease in the ratio $\mathrm{CBF}_{pathologicalarea}/\mathrm{CBF}_{cerebellum}$. The maximal change is reached between 10 to 15 min post injection.

5.2.2 Single Cases: Continuous Recognition Task

Introduction

The constant infusion method does not seem to be suitable for evaluation of complex cognitive functions, as the background noise due to the low dose of applied radioactivity (maximal radiation dose must not exceed 4–5 mSv) is high. We performed a pilot study with four subjects using the continuous recognition paradigm as described in chapter 4 in a blocked–event related design. Blocks of the recognition task were presented alternating with long blocks of an easy to perform baseline task. Only in two out of the four subjects a statistically significant result could be obtained.

Task

We presented the same 35 coloured photographs during 4 trials (Figure 5.1). The volunteers had to recognize repetitions of the pictures within the current trial. Before scanning, the volunteers performed practice trials, which used the same photographs. Consequently, during the scanning time (50 min) subjects performed the same task in which the spontaneously confabulating patients had failed. The same type of task activated in previously performed group study (see 4.2) the orbitofrontal cortex. In between the 4 trials, a baseline task had to be performed to allow the signal in the orbitofrontal cortex to decrease again. The baseline task was an easy recognition task, the volunteers had to respond when the coloured random–dot stimulus appeared, and should not respond when a uniform blue or green stimulus was presented. In order to prevent any possible interaction with the main task, we used a

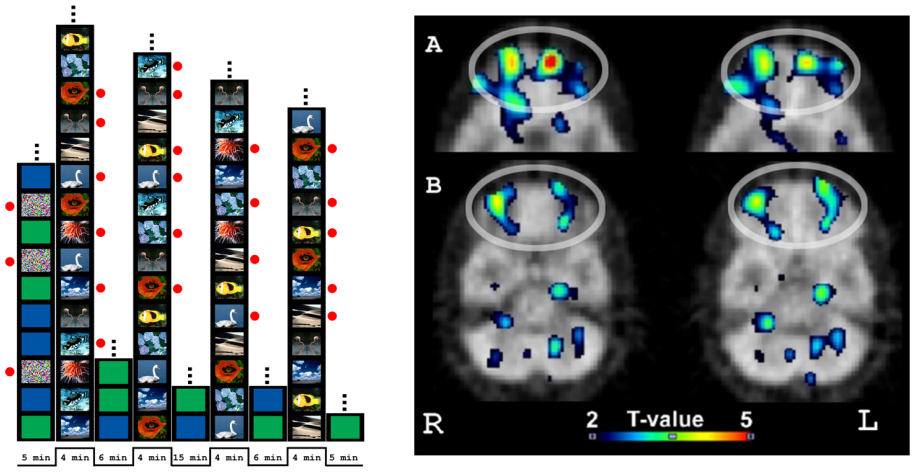

Figure 5.1: Left side: This figure displays the design of the event related PET study. During 4 minutes, the subjects perform a continuous recognition task. In this scheme, red dots indicate targets. In between the trials the subjects perform a baseline task. The target was a random dot stimulus. Green and blue displays were randomly presented as distracters. Right side: shows the results of the first two volunteers. The regions with significantly ($p < 0.01$) increased regional cerebral blood flow regions during the repeated performance of the continuous recognition task were overlaid on the individual PET–images. The OFC is highlighted.

random–dot pattern instead of a photography.

Each trial of the main task was presented for 4 minutes, with 6 minutes of baseline task between trials. During 15 seconds one cerebral blood flow image was acquired. In total 200 images were acquired in the 50 minutes of experiment. Baseline task duration had to be slightly increased in the middle of the experiment, as the current scanner software is not able to acquire more than 100 images at once. A reset time of the scanner for about 4 minutes had to be accepted as well as a following 5–minute baseline at the beginning of the second part, to obtain the actual baseline signal again.

Results

The preliminary results clearly show that activation of the orbitofrontal cortex with this paradigm in a single subject is observable. However, only in two of the four pilot subjects a satisfactory result could be obtained. Figure 5.1 shows the significantly ($p < 0.01$) higher activation during the performance of the continuous recognition task of the first two volunteers.

Discussion

One problem of the constant infusion technique is noise in the signal, which can be up to 6% (Weber et al., 2004). This is comparable to the difference in CBF we can expect using a cognitive paradigm. Nevertheless, the technique is especially promising for single event related PET in case of strong activations. Typical examples for such tasks are motor activity versus rest or language task such as stem completion or picture–word matching versus rest, which we use in clinical routine for preoperative evaluations.

Chapter 6

Memory Studies

All of the studies presented here were performed with healthy male students and approved by the local ethical committee and by the Swiss federal office of radioprotection. The three studies presented and discussed in the current chapter using the continuous recognition task as described before (see 4) in different variations. The first study is already published in a different version than presented here (Treyer et al., 2003a).

6.1 Subcortical Loop Activation during Selection of Currently Relevant Memories

6.1.1 Introduction

Occasionally actions of brain–damaged patients are based on previous habits rather than on true ongoing reality. They justify their behaviour with stories that appear invented but can be traced back to real events (spontaneous confabulations). Clinical studies showed that these patients fail to suppress activated memory traces that do not pertain to ongoing reality (Schnider and Ptak, 1999). Their lesions always involve the anterior limbic system, in particular lesions or disconnection of the orbitofrontal cortex (OFC). The aim of the first $H_2{}^{15}O$ PET study in healthy male subjects was to show activation of the OFC during the task, which the spontaneous confabulating patients failed in (Schnider et al., 1996a). An evoked potential study had furthermore shown that this suppression mechanism is cortically represented before the stage of recognition (Schnider et al., 2002). The aim of this study was to show through what anatomical connections the OFC might exert this inhibitory influence on the neocortex.

6.1.2 Design

Eight male right–handed subjects (aged 20–31) took part in this study.
To measure the ability to suppress currently irrelevant information the same continuous recognition tasks as in the PET study described in section 4.2 was used. The task consisted of three runs, displaying the same pictures in different orders. The instruction was the same: to detect repetitions in the current run irrespective of what had happened in the runs beforehand.
Currently relevant information is defined by the previous appearance of a stimulus within the same run. In the first run all stimuli are initially new, so an item appearing familiar in the ongoing run could be assumed as a repetition, i.e. a target. The performance in the first run depends primarily on new learning. In the two subsequent runs all items are familiar, the subjects have to distinguish between appearance in the present ("now") and in previous runs ("past") and cannot rely anymore on familiarity. The task is to select relevant information, i.e. repetitions in the current run, and concomitantly to suppress currently irrelevant memories such as previous repetitions in past runs.

Conditions

In this study four different sets of stimuli were applied, in order to have multiple blocks of the tasks. The sets consisted either of concrete nouns, pronounceable nonwords, meaningless geometric designs and line drawings of objects (Snodgrass and Vanderwart, 1980). The sequence of the four sets was counterbalanced over the subjects. In every run the subjects saw 60 items consisting of 40 different items, of which 12 reappeared once or twice. Every stimulus was presented on a screen above the subjects for 3 seconds with an inter–stimulus interval of 1 second. A stimulus repetition within a run had to be indicated by pressing a button with the right thumb. When a stimulus appeared the first time within a run no button had to be pressed.
The same 40 stimuli were presented in all three runs. There was a break of 90s between the runs. The order of the items of a set was different in every run. In the second and third run different but also same stimuli as in the preceding runs could repeat, i.e. be targets. In the subsequent runs of each set the subjects were asked to forget that they had already seen all pictures and to indicate picture recurrences solely within the present run.
Prior to the tests in the scanner the subjects performed one test run with photographs as used in the study described in section 4.2.

Cerebral blood flow was measured in the first and third run. The second run served to increase the subjects' familiarity with the stimuli and as washout period of radioactivity. The subjects performed the baseline task 6 min after the third run of every block. The four baseline tasks consisted of the repeated presentation of two different stimuli out of the four stimuli groups, with intermittent immediate picture recurrences whose frequency was similar to target presentations in the activation task. The subjects indicated the targets by pressing the button with their right thumb. So the baseline tasks were similar to the activation tasks in terms of the visual complexity of the presented items and the type and frequency of responses. However, they differed from the activation tasks as they had virtually no memory component; recognition of immediate picture repetitions is very simple, including task instructions.

6.1.3 Results

Behavioral Results

Tables displaying the reaction time and hit statistics are presented in the appendix A. Overall the subjects performed well. The hit rates differed only slightly (not sign., Kruskal Wallis test: χ^2=0.56, df=2, p=0.76). The reaction times between the three runs showed no significant difference in the GLM analysis for repeated measurements in the time effects (F(2,6)=2.65, $p > 0.15$) but within subjects (F(2,14)=4.02, $p < 0.05$). A further analysis of variance revealed a significant contrast between the first and the second run but not between the first and the third run as well as the second and the third run (R1 vs. R2: F(1,7)=5.96, $p < 0.05$; R2 vs.R3: F(1,7)=0.01, $p > 0.05$; R1 vs. R3: F(1,7)=4.44, $p > 0.05$).

Regional Cerebral Blood Flow Changes

The coordinates and statistical parameters of the significant activations are summarized in the tables 1 and 2 (appendix A).

Contrast of First Run Relative to Baseline Areas with significantly increased blood flow in the first run relative to the baseline are depicted in Figure 6.1(A). Performing the first run, which requires new learning, revealed a significant increase in the hippocampal–parahippocampal region and the fusiform gyrus bilateral compared to the baseline task. A significantly increased blood flow was also found in the right OFC, to a lesser degree in the left OFC, bilaterally in the anterior insula and in the areas from the ventral tegmentum to

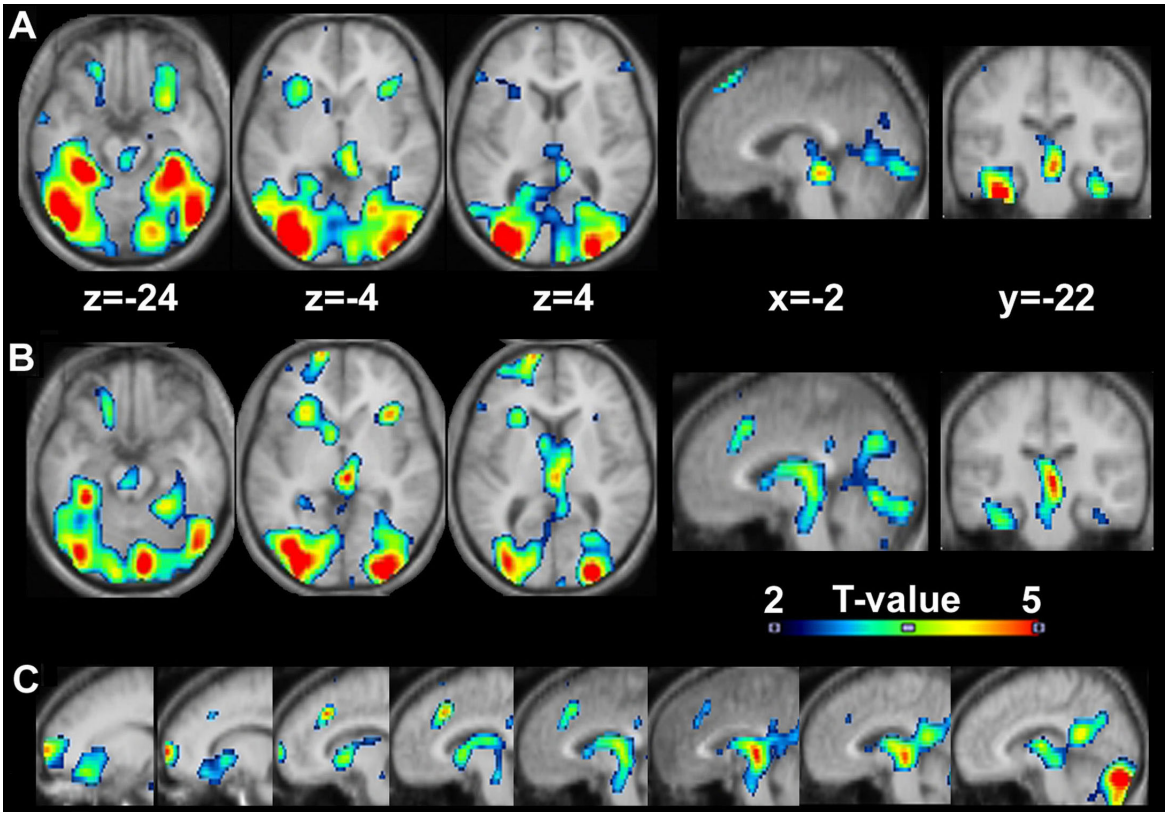

Figure 6.1: A) Contrast of first run minus baseline. B) + C) Contrast third run minus baseline.

the posterior thalamus.

Contrast of Third Run Relative to Baseline The main interest in this study was the activation during the third run. The expected activations were in the OFC and subcortical areas. The clusters with significantly increased blood flow in the third run relative to the baseline are depicted in Figure 6.1A. Significantly increased blood flow was found in the substantia nigra, dorsal medial thalamus, left caudate, left and right anterior insula and left and right OFC (Figure 6.1C). Significant results in the orbitofrontal and medial regions of the brain, according to our a priori hypothesis, are summarized in table 1 (appendix A). The dorsal medial thalamus activation was significant at a level of $p < 0.025$, corrected for the whole brain.

The main issue of this study lies in subcortical participation. To further investigate the activations of the area extending from the substantia nigra to the dorsal medial thalamus a region of interest (ROI) analysis was performed. The definition of the ROI based on the statistical parametric map revealed from the contrast third run minus baseline. The analysis of variance, upon the mean values in the ROI from the different conditions and subjects,

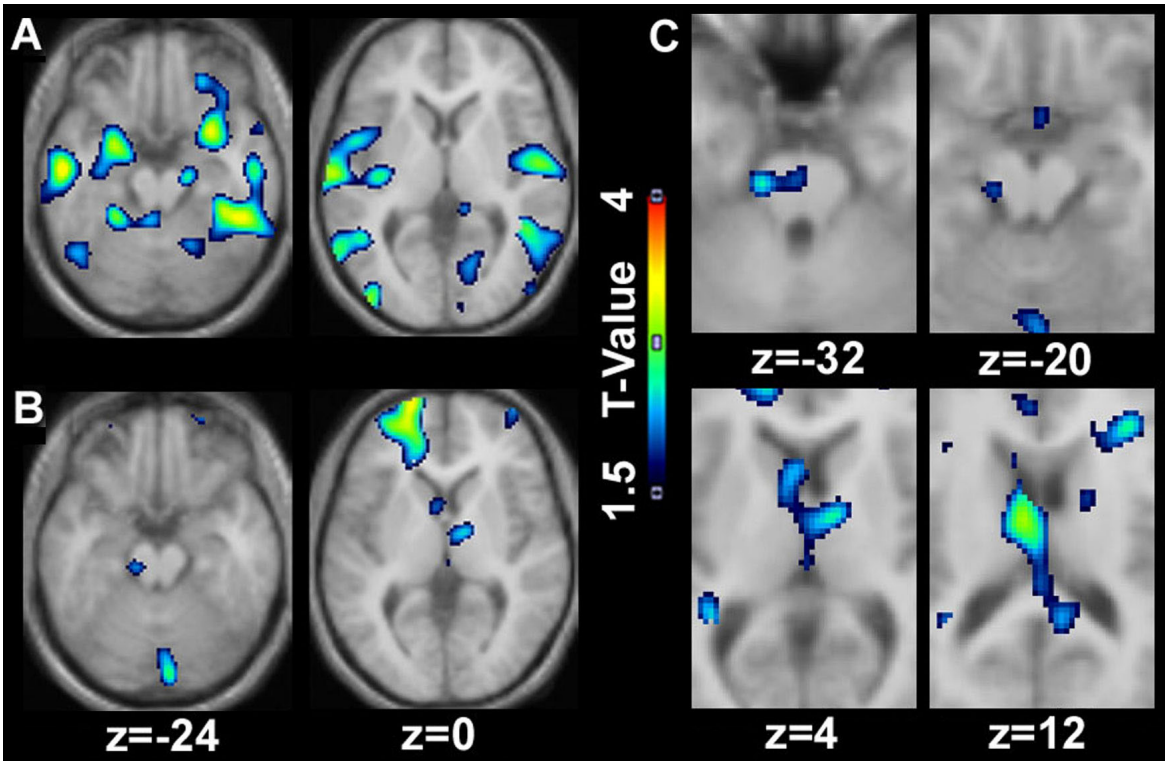

Figure 6.2: A) First run minus third run. B) + C) Third run minus first run.

revealed a significant effect of the conditions (i.e. baseline, first and third run) ($F(2,93)=5.25$; $p < 0.01$). The post–hoc Scheffe–test showed a significant effect between the third run and the baseline ($F(2,93)= 3.09$; $p < 0.05$) but not between the first run and the baseline.

Direct Comparisons To reveal the difference between the two conditions during the first and third run we performed a direct comparison. We used a lower threshold ($T > 2$ (aprox. $p < 0.025$)) to reveal also minor differences in the regions of interest in subcortical regions. And indeed, in the first compared with the third run a higher regional blood flow in perirhinal and parahippocampal cortex (Figure 6.2A) was revealed bilaterally. Also in this direct comparison the activation in the right perirhinal cortex forms an extension into the right anterolateral OFC. These findings further support the results from the comparisons with the baseline. Activations in both inferior temporal cortices (left $T=3.46$; right $T=2.78$) have to be mentioned, knowing that being outside the region of interest they do not satisfy our significance level. They are reported here because of their close relations to the posterior limbic network explored with this contrast.

The third run in relation to the first run revealed a higher perfusion in the caudate, medial thalamus, the substantia nigra and also presumably the formatio reticularis (Figure 6.2 B+C). The fronto polar activations (left $T=3.91$; right $T= 2.71$) have to be taken into

account as interesting findings. Again the findings in this contrast support the previous results comparing the third run with the baseline. There is a clear activation in the subcortical regions due to the specific activation of the third run.

Regions Co–activated With the OFC In both contrasts comparing the continuous recognition task with the baseline, the OFC was activated. Four different regions could be identified because the left (from "third run – baseline") as well as the right OFC (from "third run – baseline") activations had a more anterior and a more posterior local maximum. Based on these results we hypothesised that the OFC activations are probably based on the activations of different networks. To investigate the proposed different functional connections of these areas, a regression analysis was performed. For this purpose ROIs were defined over these clusters, as shown in Figure 6.3 (middle). The mean blood flow was calculated and used as a regressor in the analysis. Significant correlations with the left anterior ROI (A) were found in the region of the substantia nigra, the medial thalamus, the left and right body of the caudate and the left posterior insula. The right anterior OFC (B) is significantly co–activated with the left OFC, the left anterior cingulum, left caudate, the left putamen, the left perirhinal cortex, left anterior insula and the pons. The left posterior cluster (C) is co–activated together with the right OFC the left anterior putamen and the anterior hippocampal formation bilateral, in a bigger extension with the right one, whereas the right OFC (D) shows a co–activation of the left OFC and the right anterior hippocampal formation.

6.1.4 Discussion

The present study searched for a network underling the ability to suppress irrelevant memory traces. The healthy subjects performed the task well. The third run was harder for them to perform but they still showed good performance. In any case, the performance itself did not have an effect on the activations corresponding to the reality monitoring task.
The major result of this study is the activation of subcortical regions involving the substantia nigra, medial thalamus and the left caudate as well as the left insula and the left OFC in the third run compared with the baseline.
Both runs activated the OFC. The third run activated primarily the left OFC and the first one the right side. The co–activation analysis using the four OFC activation foci revealed different functional connectivities. The right OFC regions showed co–activations with the posterior left OFC. Therefore the right OFC activations might belong to the same

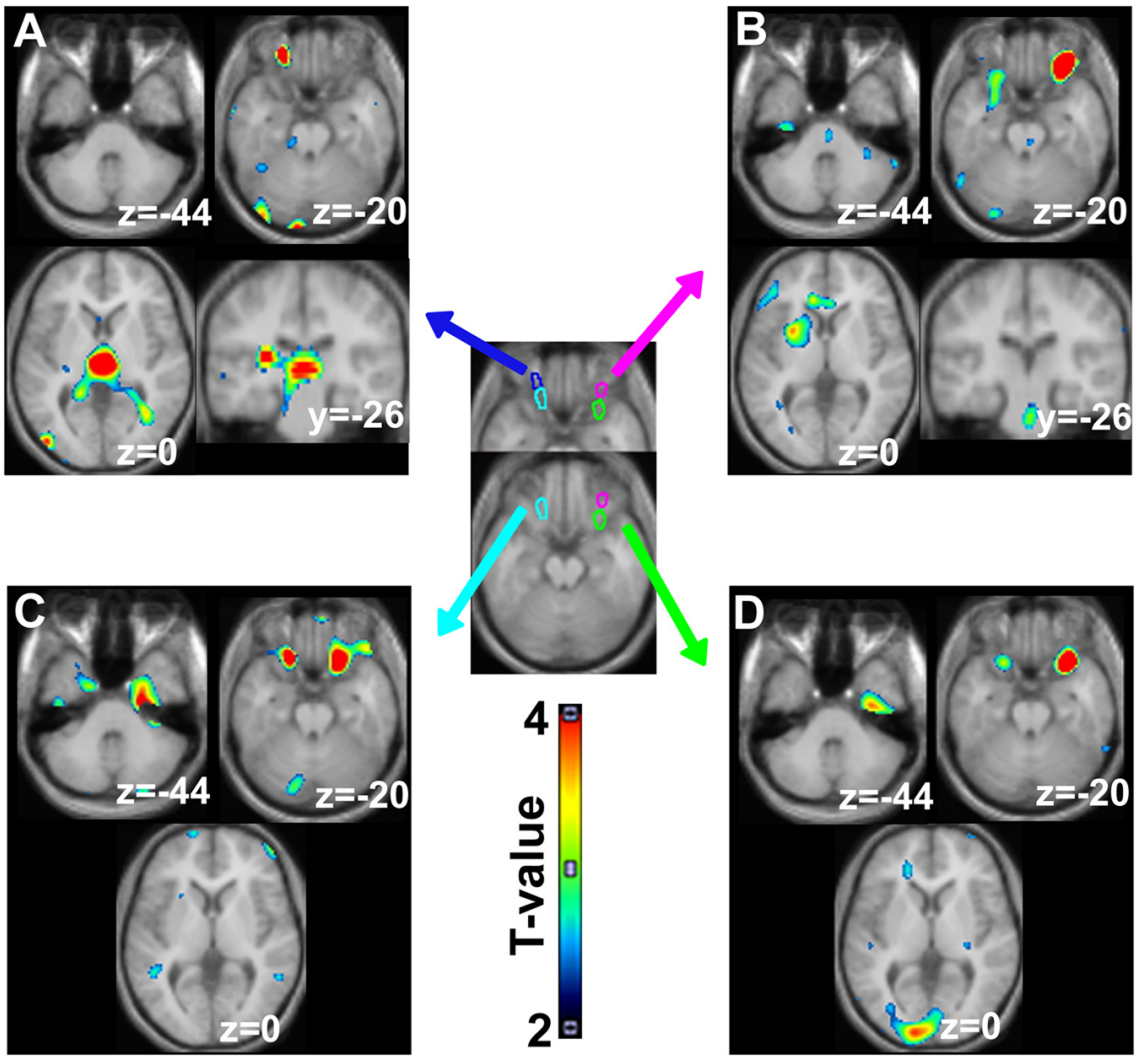

Figure 6.3: In the middle the four ROI's are displayed which were used to evaluated co–activations. The results of the simple regression analysis were displayed in the four corners.

network as the left but were probably more involved in the processing of new information as in the suppression process (Frey and Petrides, 2000). Disclosing the different parts of the activated OFC reveals co–activations with different brain regions. The more anterior parts are mainly co–activated with subcortical areas, the substantia nigra, pons and medial thalamus. The more posterior parts show co–activations with hippocampal areas. The left anterior as well as the left posterior were both activated during the third run but revealed different functional connections. This finding suggests an integration of the memory system within the monitoring system. Analysing the role of this nexus of OFC connections with the subcortical and temporal areas will require further studies, especially event–related studies with improved temporal resolution.

The first and the third run in this study both activated the mediotemporal network, but the third one to a lesser degree. This could be expected, as in both runs the memory system has to be activated in a higher degree than during the baseline. The slightly smaller activation in the third run indicates the mediotemporal system does not underlie the additional abilities required in the third run.

The central point of this study is the participation of subcortical regions during a task, which requires monitoring of ongoing reality. The activated regions, medial thalamus, caudate and substantia nigra are part of a dopaminergic modulated fronto–subcortical loop (Alexander et al., 1986). Monitoring of ongoing reality is based on the activation of this fronto–subcortical loop. If parts of the OFC are damaged monitoring ongoing reality could fail, as seen in spontaneously confabulating patients (Schnider, 2003).

Some of the activated clusters are also found in different reward–related studies. The OFC is known to be relevant e.g. in reward–discrimination tasks in monkeys (Schultz et al., 2000) as well as in reward–related tasks in humans (Thut et al., 1997; Elliott et al., 2000; O'Doherty et al., 2001a). Besides prominent OFC activation, reactions in the basal ganglia were also found in humans (Brown et al., 1999; Delgado et al., 2000). More direct evidence for the involvement of the striatal dopamine system in reward was revealed in a human raclopride PET study using a video game task (Koepp et al., 1998). Extinction studies in monkeys, where habits were rewarded in a first part and afterwards no more, neuronal responses were revealed in similar regions as our third run did (Rosenkilde et al., 1981; Thorpe et al., 1983; Schultz et al., 1998). These regions seemed not only to be involved in reward monitoring, but also in reality monitoring and therefore in the ability to refer thinking to ongoing reality.

6.2 A Non–Matching Task Variant

6.2.1 Introduction

The results presented so far could not exclude the possibility that the observed activations during the recognition task were a mere consequence of the go/no–go design, since our subjects do not press a button when a non–target appears. Indeed, several studies had shown that parts of the OFC seem to be involved in response inhibition (no–go)(Jones and Mishkin, 1972; Kowalska et al., 1991; Casey et al., 1997; Fuster, 1997). Using a go/no–go paradigm, Casey et al. (1997) (Casey et al., 1997) found OFC (BA11) activation related to motor inhibition. More successful inhibition of inappropriate responses resulted in a higher activation in the OFC.

Elliott and Dolan (1999) have shown in an fMRI study different orbitofrontal activations during a delayed–matching–to–sample (DMTS) and a delayed–non–matching–to–sample task (DNMTS). During these tasks a test stimulus was presented for one second and after a delay two choice stimuli appear. The subjects had to choose either the matching or the non–matching stimulus. During the DMTS compared to the DNMTS condition they found an increased activation of the caudate and the medial OFC. The DNMTS task was associated with activation in the lateral OFC and medial thalamus. The authors suggested that the difference in the OFC activation arose from necessary inhibition of the response to the familiar stimulus in the DNMTS task. But the results of this experiment have to be interpreted with caution due to artefacts in the orbitofrontal regions, which typically occur with scanning parameters used in their study.

Our continuous recognition task is loosely related to a DMTS design in that a stimulus is at the same time test stimulus and potential target. On the other hand, during the delay period between the first and the second appearance a different number of other potential target or distracter stimuli appear, and have to be held on–line. In the subsequent runs of the task monitoring of ongoing reality is needed, to prevent false positive responses to distracter items (first appearance in the ongoing run).

The same task can also be performed akin to a DNMTS design. Subjects have to respond to the first appearance in the ongoing run but not to the reappearance of the stimulus. This task needs to inhibit reactions to the familiar items (in the first run) or the repetition of an item (in the second and third run). If the previously reported OFC activation were due to inhibition of responses, the same activation should be stronger during the DNMTS version of the task.

It is known that task switching, which would occur when the same subject has to perform both tasks one after the other, activates frontal cortex regions (Aron et al., 2004). It has been shown that even fast switching from one motor response mode to another can lead to an inhibition of the previous strategy and subsequently to longer reaction times (Koch et al., 2004). Switching from one strategy to another especially when reward is given to the correct choice the OFC plays a major role, as imaging and clinical studies have shown (O'Doherty et al., 2001a; Hornak et al., 2004). Furthermore, task switching, including change of behavioural reactions from response to suppression mode, in this case switching between GO (reaction at stimulus onset) and WAIT (reaction at offset), causes changes in event related electrical potentials in the frontal cortex (Swainson et al., 2003). To be able to attribute in this experiment frontal cortex activation to the respective task demand, may it be selection of currently relevant memory information as needed in the third run or motor inhibition as in a higher degree needed in the DNMTS version of the task, we used a two–group study design.

6.2.2 Design

Our "DNMTS" and "DMTS" tasks described in this section were identical to the previously described continuous recognition task apart from the following exceptions: Subjects perform just one block of three runs of either DMTS or DNMTS. For a better comparability the relation of distracter to target was 1:1 in this experiment, so that in both conditions (DMTS and DNMTS) the number of true positives will be the same, and also the behavioural demand of pressing the button. Hence, the only difference between the two conditions was the instruction, as to press when an item reappears in the ongoing run (DMTS) or to press when an item appears the first time in the ongoing run (DNMTS).

Each stimulus was presented for 3 seconds with an interstimulus interval of 1 second. Overall 35 different coloured photographs were presented. They consisted of landscapes, vehicles, flowers, animals or trees. There were 25 targets and therefore 25 repetitions. Every stimulus only reappeared once within a run.

Two groups of 10 male students each participated in this experiment. One group performed the DNMTS, the other group the DMTS task.

6.2.3 Results

Behaviour

Tables displaying the reaction time and hit statistics are presented in the appendix A.

Group DMTS The hits only differed slightly (not sign.: Kruskal–Wallis χ^2=3.0,df=2, $p > 0.1$) between conditions. The reaction times (only true positives) between the three runs did not show a significant difference in the GLM analysis for repeated measurements in the time effects (F2,8=4.34, $p < 0.05$) but a significant within subject effect(F(2,18)=6.50, $p < 0.01$). A further analysis of variance revealed a significant contrast between the first and the second and the third run, but not between the second and third run (R1 vs. R2: F(1,9)=7.52, $p < 0.05$; R1 vs. R3: F(1,9)=9.21, $p < 0.05$; R2 vs. R3: F(1,9)=0.04, $p > 0.05$).

Group DNMTS One has to consider that this group performs 10 button presses more at the beginning, whereas the other group does not press the button during this first part. Therefore the 10 first pictures and their reaction measurements during the recognition task were discarded for comparison reasons. The hits only differed slightly (not sign.: Kruskal–Wallis χ^2=2.1, df=2,$p > 0.1$) between conditions. The reaction times (only true positives) between the three runs did show a significant difference in the GLM analysis for repeated measurements in the time effects (F(2,8)=17.71, $p < 0.001$) and within subject (F(2,18)=10.88, $p < 0.001$). A further analysis of variance revealed a significant contrast between the first and the second and the third run, but not between the second and third run (R1 vs. R2: F(1,9)=26.97, $p < 0.001$; R1 vs. R3: F(1,9)=15.07, $p < 0.005$; R2 vs. R3: F(1,9)=0.54, $p > 0.05$).

Comparing the Groups Comparing the reaction times (only true positives) between groups revealed a significant result in the GLM analysis for repeated measurements in the overall time effects (F(2,17)=19.37, $p < 0.001$), but not for the interaction of time and group effect (F(2,17)=1.49, $p > 0.05$) and between subjects effects (F(1,18)=0.86, $p > 0.05$). Both groups did show similar reaction times in the different conditions.

Regional Cerebral Blood Flow Changes

The tables displaying the statistical outputs are presented in appendix A. The tables show all activations of the mentioned contrast with a cut–off of T>3. Some regions were mentioned even though they do not reach the cut–off level, in the case of if they show activation in

a different contrast or group, for comparison reasons. Figure 6.4 displays the statistical parametric maps with a cut–off of T>3 overlaid on an average MR anatomy, as in the study reported in section 6.1.

Contrast of First or Third Run Relative to Baseline for each Group Overall we found strong activations in both groups. Comparing the first run with the baseline revealed clear left and right hippocampal and parahippocampal activations in both groups. OFC activation has already been observed in the first run of both groups on the right side. Only the DMTS group showed OFC activation also on the left side.
The comparisons of the third runs with the baseline revealed smaller and less significant activations in the mediotemporal regions for both groups. Clear OFC activations were seen in both groups, but especially in the DNMTS group.
Comparing the activations in the OFC in all four contrasts, the activations in the third runs are more ventrally placed (z=–32) whereas in the first runs more dorsal (z=–12/–16).

Direct Contrasts Between the First and Third Run for each Group Regarding the direct contrasts of the first run minus third run a mediotemporal activation in the DNMTS group and a less clear one in the DMTS group is visible. The contrast third run minus first run showed no mediotemporal activation but in both groups a left OFC and in the DNMTS group also a right OFC activation.

Comparing the Groups The group comparisons showed an overall stronger activation in the DNMTS group in both conditions, in the first as well as in the third run. Stronger activation in the polar frontal cortex were present, but non in the OFC. An impressive difference has also to be noticed in the caudate, which was more activated in the DNMTS group during both runs.

6.2.4 Discussion

First, there was no significant difference in the OFC activation between the two groups. Therefore our data do not show a clear relation between the OFC and response inhibition. A region more closely related to motor inhibition seems to be the caudate, which was more activated in the DNTMS group. It is known that the caudate is part of the motor system and also relevant for cognition (Aron et al., 2003; Booth et al., 2003). In the experiment of Elliot and Dolan (1999) the DMTS task activated the caudate more strongly. Their inter-

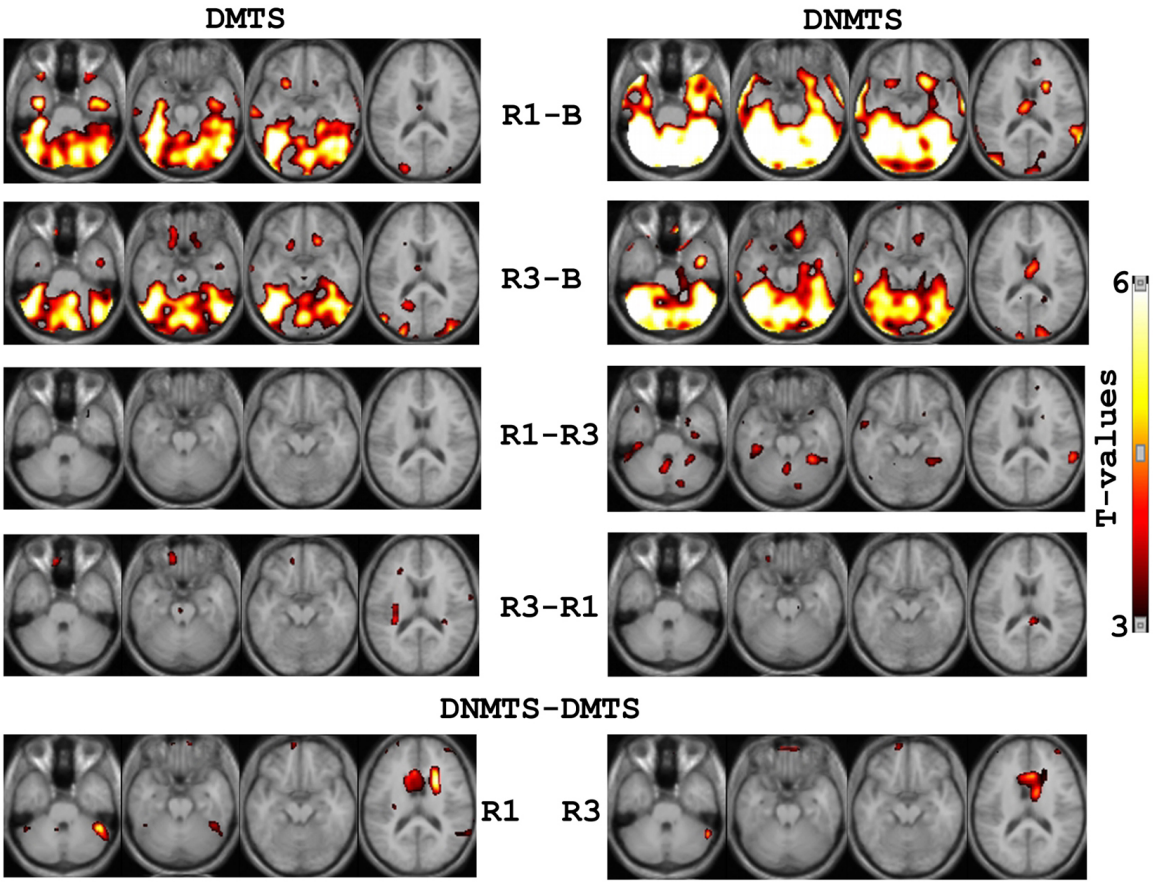

Figure 6.4: Shows the results of the two groups (upper part) and the comparison between groups (lower row). R1 = first run; R3 = third run; B= baseline; DNMTS = group performing the non–matching version; DMTS = group performing the matching versions.

pretation of the medial OFC and left caudate activation during DMTS had been primarily based on the findings on responses to stimuli that signal behavioural responses (Rolls et al., 1994; Rolls and Treves, 1994). Such a stimulus–response association should arise in their DMTS condition but not in their DNMTS, where the reaction is not oriented to the sample stimulus, which would be the prepotent reaction. Their DNMTS did in contrast activate the lateral OFC as well as left thalamus and left premotor cortex. Our task is far more complex due to its continuous design, without decision breaks after each presentation as in the Elliot and Dolan study. A direct comparison is not possible. We could not find a difference in the OFC activation at all between the DNMTS and DMTS tasks as they did. Furthermore, the OFC activations in the baseline comparisons did not differ in their position as the findings of Elliot and Dolan would propose (lateral OFC during DNMTS and medial during DMTS). Behaviourally the reaction times in the DNMTS group were slightly longer but not significantly. Asking the subjects about their subjective impression afterwards, subjects of the DNMTS group thought that they struggled more than subjects performing the matching version. In infants and monkeys (Gaffan et al., 1984) the opposite is the case, for both of them the detection of the novel compared to detection of the familiar is easier.
The comparisons within group showed again the same activation pattern as in the study before. We found OFC activation predominantly in the third run and mediotemporal activations during the first run. Nevertheless the OFC activation was stronger in the DNMTS group. But as the overall activation in the comparisons within the DNMTS group was stronger also this activation could be attributed to difficulty or higher inconvenience of the subjects with the DNMTS version of the task.

6.3 Auditory Stimulations

Up to now we have shown that OFC activity serves a filter function needed to monitor ongoing reality in the visual domain. Here we address the issue, whether this function depends on the modality. In the experiments reported in this section we tested different auditory stimulations to reveal a modality independent function of the OFC.

6.3.1 Introduction

Most studies that investigate the human hippocampal memory system use visual stimuli, but only few are concerned about auditory memory. Lesion studies of hippocampus and rhinal cortex on dogs (Kowalska et al., 2001) and monkeys (Saunders et al., 1998; Fritz et al., 1999)

revealed no impairment or functional loss in an auditory delayed–matching–to–sample task using delay intervals up to 90s, whereas a visual delayed–non–matching version of the task revealed an impairment after the retention especially of the rhinal cortex (Meunier et al., 1993; Baxter and Murray, 2001). In human patients two widely used tests to measure verbal memory functions are auditory (AVLT and CVLT). Both tests detect diminished verbal memory function in left (language dominant) sided hippocampal lesioned patients very well (Gleissner et al., 2002; Banos et al., 2004). Recent event–related fMRI studies in healthy humans also showed a relationship between predominantly left hippocampal activation and auditory verbal memory (Saykin et al., 1999). The left anterior hippocampus was activated while novel words were presented during this recognition task, whereas the left posterior parahippocampal region was activated during detection of previous learned words. Furthermore, a positive correlation of these fMRI results with the clinical CVLT test could be shown (Johnson et al., 2001). Another study concerning explicitly the encoding of auditory presented word lists showed long–term sustained bilateral responses of the hippocampus and parahippocampus (Kato et al., 1998).

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In the studies presented beforehand, we have shown a dissociation of orbitofrontal cortex

and hippocampal formation activation due to the repetition of a continuous recognition task. All these studies used visual stimuli of different complexities, such as line drawings of objects non pronounceable geometric designs, words and non–words as well as a variety of coloured photographs.
We tested in these memory experiments if this distinction between orbitofrontal and hippocampus formation functions shows the same dissociation using different kinds of auditory stimuli, such as natural environmental sounds as well as spoken words.

6.3.2 Design

The subjects were 29 male right–handed students. We performed three experiments in succession. In the first experiment eight subjects performed the continuous recognition task with natural sound stimuli. In everyday life we do not have to deal with short natural sound clips taken out of their context to the same degree as we deal with words or pictures. To explain the results of the first experiment and to test if the low familiarity with this kind of stimuli is a major drawback we performed a second experiment with 10 different subjects participating. The subjects were prior to scanning familiarized with the sound stimuli, to allow the subjects to associate a meaning for every sound clip and probably to ease the discrimination in the continuous recognition task. To reveal if the results of this two auditory experiments depended on the special type of stimuli used or if it is the use of the auditory modality, we performed a third experiment with 12 subjects using acoustically presented nouns.

Stimulations

In all three experiments subjects performed a continuous recognition task as used in the earlier PET studies. Several parameters of the task were modified. First and obviously instead of visual items such as colored photographs, line drawings of objects, abstract designs, words and non–words we used auditory stimuli such as natural sounds (animal voices, street noise, raindrops etc.) and spoken common German words. As our auditory stimuli were not all of exact equal length and especially natural sounds have a typical fade–in or fade–out, we displayed during the auditory presentation a white border on a CRT monitor to define the presence of the stimulus and the time window in which a response can be given. In all experiments the interstimulus interval was one second during which a fixation point was presented in the middle of the screen.

Secondly, in the current study 35 stimuli were presented, of which 25 reappeared during a run and were therefore targets. (In the visual studies the task consisted of 40 images and 20 reappearances). Finally, the presentation duration of the stimuli was three seconds (as in the visual studies) only in the experiment using natural sound clips. The third experiment using spoken German words was conducted with two seconds stimulus presentation due to the short duration of the chosen words.

Task

The continuous recognition task consists of three runs. For all runs the same instructions was given: "press the button of your device when a stimulus reappears within the current run."
During the first run encoding of new stimuli as well as distinction of novel and familiar stimuli had to be made. During the forthcoming runs all stimuli were familiar, the subjects had to select and react on only the repetitions of the current run and could not anymore judge on familiarity. In the second experiment the subjects were familiarized with the sound clips beforehand, but during the first run, the stimuli occurred the first time in the context of a recognition task. Nevertheless the first run of the second experiment has to be interpreted carefully.

Natural Sound Clips The sound clips were downloaded from different sources on the internet and post processed with creative wave studio 4.21.07 (by creative technology ltd.). All clips were normalized with respect to their amplitude and shortened to a 3 second clip. Three different lists were made to cover the variety of natural sounds and to circumvent an impact of a single clip, as this study is not about auditory perception per se. All lists included the same amount of animal voices (elephant, cat, dog, cow, etc.), every day household noises (knocking on doors, clock ticking, a bite into an apple, etc.), as well as machine noise (shaver, drill, chainsaw, etc.), vehicle sounds (cars, planes, trains, etc.) and also environmental sounds, such as raindrops.
In the first experiment the participating 8 subjects had not heard the sound clips beforehand. The subjects from the first experiment subjectively experienced some trouble with the sounds, and had therefore already problems in distinguishing the sounds from each other in the first run. In the second experiment another 10 subjects listened to the sound clips three times beforehand. In these familiarisation trials every sound clip was presented twice

in succession to allow the subject to familiarize and learn to discriminate them.

Word Lists The words for the third experiment were chosen from the 10'000 most used German word list from the web–page: http://wortschatz.uni–leipzig.de. This list comprises popular words including several cases, singular and plural, capital and lower case letters as single entries. We assembled two lists of words. One half of each list consisted of concrete nouns such as coffee, cow, knight and the other half of abstract nouns such as month, project and freedom. All words were spoken into a microphone by the author and qualitatively tested for comparable quality, loudness and pronunciation. All clips were shorter than two seconds.

Image Statistics

The difference among the conditions was evaluated voxel by voxel in a PET multi–subject design. We accepted significance in the a priori defined regions (mediotemporal lobe and temporal cortex) when $p < 0.001$, uncorrected for multiple comparisons. To test for common and typical activations in all three experiments two conjunction analyses were performed (Friston et al., 1999) one with the contrast first run–baseline and one with third run–baseline contrasts.

Behavioral Analysis and Correlation with Image Data (as used in Auditory Experiments) Statistical analysis of the behavioral results were evaluated with SAS 8.2 using the Kruskal–Wallis test for the comparisons on the Wilcoxon scores of the hit rates and the GLM procedure for repeated measurements for the reaction times comparison for the continuous recognition task. The behavioral results for the baseline were perfect with only minor failures as expected from the ease of the task.
To test for a possible coherence between cerebral blood flow and reaction times between subjects we made a pixel wise simple correlation analysis at a level $p < 0.001$ (uncorrected) for each condition separately. We did not test for reaction time effects between conditions as in most of the subjects the reaction times were similar (no sign. differences between reaction times of first run and third run in all experiments) between the runs of the continuous recognition task. Single subjects with clear differences would in this case bias the statistics especially at this rather small number of participants per experiment. For a post hoc correlation analysis on region of interest (ROI) data we defined the ROI around the cluster at a cut–off $p < 0.001$ and only on the slice with the maximal activation using PMOD. On the data we performed a Pearson correlation and Wilcoxon analysis using SAS 8.2.

6.3.3 Results

The subjects performed well in all three experiments. The behavioural results are displayed in appendix A.

The tables displaying the statistical outputs of the SPM analysis are presented in the appendix A. For the regions of interests, i.e. temporal and frontal lobe as well as thalamus, basal ganglia and brainstem, a cut–off of $p < 0.001$ uncorrected for multiple comparisons and for the other regions a $p < 0.5$ corrected for multiple comparisons was chosen.

The Figure 6.5 shows the contrasts of the three experiments. Four different transversal slices are shown (at z = –36; –24; –16; 4) The cut–off was chosen to be $p < 0.01$ (not corrected for the whole brain volume) for all of the contrasts. The pictures show more activation than the corresponding tables do, to provide a broader base for comparisons between the experiments.

Experiment 1

Behavioral The correct responses in the three runs did only differ slightly but not significantly (Wilcoxon scores tested with Kruskal–Wallis method: χ^2=0.0323, df=2, p=0.984). The reaction times between the three runs showed a significant difference in the GLM analysis for repeated measurements in the time effects ($F(2,6)=5.96$, $p < 0.05$) and within subjects ($F(2,14)=5.90$, $p < 0.05$). A further analysis of variance revealed a significant contrast between the second and the third run, but not between the first and the second run as well as between the first and the third run (R1 vs. R2: $F(1,7)=1.28$, $p > 0.05$; R2 vs. R3: $F(1,7)=13.85$, $p < 0.01$; R1 vs. R3: $F(1,7)=4.28$, $p > 0.05$).

Regional Cerebral Blood Flow Changes

Behavioral Correlation Analysis The regression analysis of the conditions with the respective reaction times of each subject did not reveal significant activations in the regions of interest.

Contrast of First or Third Run Relative to Baseline The first experiment showed a dissociation between temporal cortex and left OFC activation. The former was activated especially during the first run whereas the latter was activated during the third run. The left OFC activation was also elicited during the first run.

Thalamic activation was seen in the first run minus baseline, while caudate and midbrain

activation was only seen in the third run minus baseline contrast. Clear activation outside the regions of interests were found in the right secondary visual cortex (BA18) during both runs compared to the baseline, in the right anterior cingulate gyrus during the first run and the right cerebellum during the third run.

Direct Comparisons (first run vs. third run) Mediotemporal regions were activated during the first run, whereas the OFC was activated during the third run. But the first run did also activate left ventral frontal region (BA 25) and right superior frontal gyrus (BA 8) as well as the right fusiform gyrus.

Transition to Experiment 2 In first experiment subjects had difficulties with the task and especially with discrimination of the sounds. We found in both runs OFC activations. One possible interpretation may be the difficulties the subjects had especially in the first run, in which they were confronted the first time with the variety of the sound clips. We therefore designed a second experiment, in which we gave the subjects the possibility to familiarize with the sound clips.

Experiment 2

Behavioral The hits only differed slightly but not significantly (Wilcoxon scores tested with Kruskal–Wallis method: χ^2=0.1607, df=2, p=0.923) between the three runs. The reaction times between the three runs did not show a significant difference in the GLM analysis for repeated measurements in the time effects ($F(2,8)=0.07$, $p > 0.05$) and within subjects ($F(2,18)=0.07$, $p > 0.05$). A further analysis of variance revealed a significant contrast between the second and the third run, but not between the first and the second run as well as between the first and the third run (R1 vs. R2: $F(1,9)=1.28$, $p > 0.05$; R2 vs. R3: $F(1,9)=13.85$, $p < 0.01$; R1 vs. R3: $F(1,9)=4.28$, $p > 0.05$).

Regional Cerebral Blood Flow Changes

Behavioral Correlation Analysis Also in this second experiment a regression analysis of the conditions with the respective reaction times of each subject did not reveal significant activations in the regions of interest.

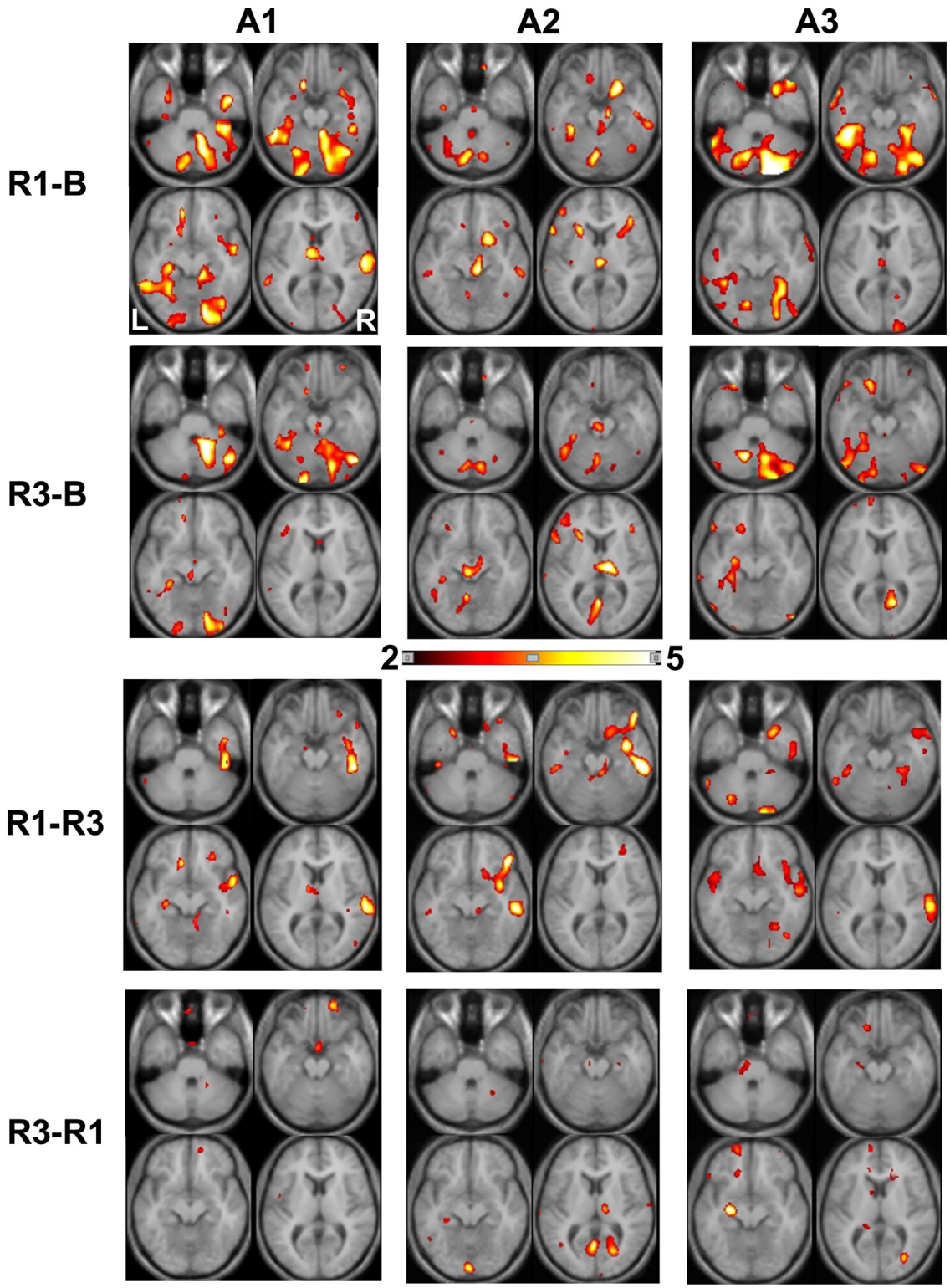

Figure 6.5: shows the results of all three auditory experiments (A1, A2 and A3). The two upper rows show the baseline contrasts, the last two rows the direct comparisons each with a cut–off $p < 0.01$). R1 = first run; R3 = third run; B = baseline.

Contrast of First or Third Run Relative to Baseline The second experiment showed activation of the temporal regions as well as OFC in both contrasts. The left uncus was activated during the first run, whereas the right parahippocampal gyrus during the third run. The OFC activations during the first run were strong and bilateral, during the third run only the left sided activation did show up again.
The right thalamus was activated even after whole brain correction during the third run. Caudate and midbrain activation was seen in the first run. During the first run left and right cerebellum were activated.

Direct Comparisons (First Run vs. Third Run) The OFC was not activated in neither of the two contrasts. The left hippocampus was stronger activated during the third run compared to the first run, whereas the first run did activated superior and inferior temporal gyrus (BA 20 and BA38). Prefrontal regions were activated in both contrasts. Thalamus and cerebellum revealed stronger activation during the third run, but right midbrain region seemed to be stronger activated during the first run.

Transition to Experiment 3 The prior presentation of the sound clips did not clarify the previous results. We therefore designed a third auditory experiment using easy and well known stimuli namely common spoken words.

Experiment 3

Behavioral The hits only differed slightly but significantly (Wilcoxon scores tested with Kruskal–Wallis method: χ^2=7.0755, df=2, p=0.029) between the three runs. In the first run 23 out of 25 hits were achieved, in the subsequent runs only 21, but the performance in all runs was adequate. The reaction times between the three runs showed a significant difference in the GLM analysis for repeated measurements in the time effects (F(2,9)=5.78, $p < 0.05$) and within subjects (F(2,20)=7.25, $p < 0.01$). Due to a technical malfunction the responses of the first run of subject no. 11 could not be acquired. This subject's results were discarded for the behavioural statistics but not for the imaging statistics, as the behavioural results (B=(974±167)ms , R2=(1578±319)ms and R3=(1563±188)ms) were comparable to the rest if the group. A further analysis of variance revealed a significant contrast between the first and the second run as well as between the second and the third run, but not between the first and the third run(R1 vs. R2: F(1,10)=7.32, $p < 0.05$; R2 vs. R3: F(1,10)=12.28, $p < 0.01$; R1 vs. R3: F(1,10)=0.84, $p > 0.05$)

Regional Cerebral Blood Flow Changes

Behavioral Correlation Analysis In this experiment we found a correlation of reaction times within first run in the left posterior OFC (x=–16; y=20; z=–28; T=4.96; $p \ll 0.001$) and in the third run in the right hippocampal region (x=40; y=–18; z=–32; T=9.57; $p \ll 0.001$). The region of interest analysis upon the significant OFC region did not reveal a significant correlation between blood flow values and reaction times during the first run (Pearson r=0.19;p=0.58). The region of interest analysis of the hippocampal region during the third run revealed a significant correlation with the reaction times (Pearson r=0.7; p=0.01). Comparing the five fastest subjects with the five slowest revealed also a significant result (Wilcoxon scores tested with Kruskal–Wallis method: χ^2=3.9382, df=1, p=0.0472). In this experiment subjects that needed longer reaction times to solve the third run did activate the right hippocampal region stronger. It is astonishing that the CBF of the right hippocampal region and not of the left one is correlated with the amount of time used to retrieve information and to decide.

Contrast of First or Third Run Relative to Baseline The third experiment revealed a more straightforward activation pattern. The first run minus baseline showed clear mediotemporal as well as auditory related activation in the temporal gyri and no OFC activation. Whereas the contrast between third run minus baseline revealed clear left OFC activation. Additionally a strong left hippocampal activation appears during the third run. Medial thalamus was activated during the first run as well as left fusiform gyrus and bilateral cerebellum. Left angular gyrus was activated during the third run, as well as the right posterior cingulate gyrus and the right cerebellum.
The right cerebellum and the left fusiform gyrus activation during the first run minus baseline remained significant even after whole brain correction.

Direct Comparisons (First Run vs. Third Run) The direct comparison revealed the same pattern as the contrasts with the baseline task. The first run activated several temporal regions (BA 20,22,42,38) predominantly on the right side. The third run almost exclusively activated the left OFC. As the baseline contrast has already shown, a clear activation of the left hippocampus proper is also visible during the third run.

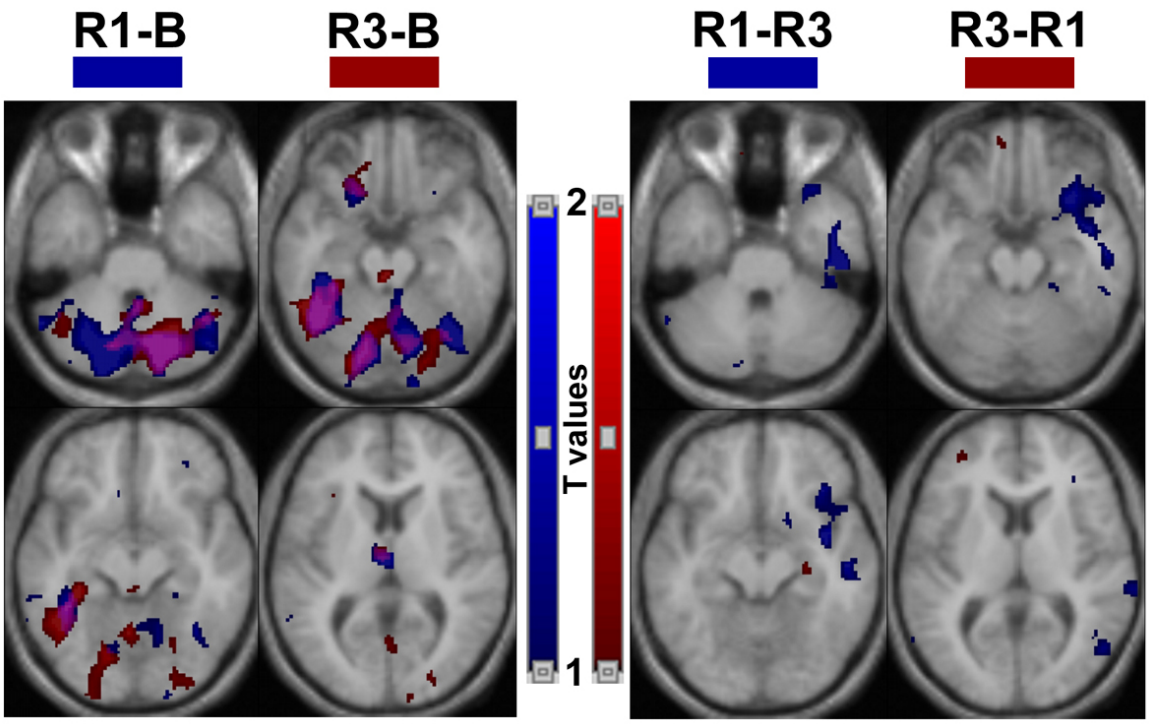

Figure 6.6: Shows the result of the conjunction analysis. The same transversal cuts were chosen as in Figure 6.5.

Conjunction Analysis of all Three Experiments

The common activation of all three experiments revealed a left posterior OFC (BA 47/11) activation during the third (coord.= –14;20;–28, T=2.14, p $\ll$ 0.001, pcorr=0.192) as well as the first run (coord.= –16;16;–28, T=2.37, p $\ll$ 0.001, pcorr=0.050) compared to the baseline in all three groups (Figure 6.6 upper left part). Furthermore the hippocampal region was activated in the first (coord.= –36;40;–24, T=3.00, p $\ll$ 0.001, pcorr=0.001) as well as third run (coord.= –34;38;–20, T=2.64, p $\ll$ 0.001, pcorr=0.009) minus baseline contrast. The direct comparisons revealed noticeable activation in the contrast first minus third run in the right fusiform gyrus (BA 20) (coord.= 50;–20;–36, T=3.02, p $\ll$ 0.001, pcorr=0.001) and a minor activation in the right OFC (BA 47) (coord.= 40;26;–16, T=2.05, p $\ll$ 0.001, pcorr=0.293) (Figure 6.6).

6.3.4 Discussion

With these three experiments we tried to reveal if the dissociation of posterior and anterior limbic system is also applicable in the auditory domain. We found in all three experiments consistent activations in the left hippocampal formation during the first run which measures

primarily the recognition of repetitions. The third run needs in addition to the recognition a filter function to separate currently relevant from irrelevant recurrences in previous runs. In the third run of a visual version of the continuous recognition task, the anterior limbic system, especially the left OFC, was activated. In the three auditory experiments the region was slightly activated during the first two experiments and somewhat stronger during the last experiment using common spoken words as stimuli. Therefore we could show that in principle the same region is activated for selection of relevant memory traces in both modalities, vision and hearing. Therefore the function of the orbitofrontal cortex as a filter is not modality specific as far as words are concerned. Using natural sounds as stimuli did not show a clear result but nevertheless in the first experiment the OFC was activated predominantly during the third run, whereas mediotemporal regions were more activated during the first run. The second experiment had no clear first run, as all subjects had already been familiarized to all sounds prior to the experiment. In the third experiment we found a strong left hippocampus formation activation we could not really explain. The left hippocampal region is related to verbal memory but why it is more stressed during the third run must be investigated further.

Overall less false positives and negatives were made during the third experiment. Also subjectively the task was easier to perform for the subjects, they did not tell any problems in discriminating the items presented, as did the subjects from the two first experiments. We chose to work first with natural sound to keep the experiment in analogy to the complex coloured photographs as presented in the DNMTS and the first PET study but it seemed that the complexity of natural acoustic scenes is experienced as more difficult. One reason may be, that the natural sound clips could not be processed as automatically as pictures, probably because our species has a more elicited visual processing system compared to the auditory or olfactory modality of other animals (Clark et al., 2001; Stevens, 2001).

Also the finding of left OFC activation already during the first run of the two experiments using natural sound clips revealed that there is something special. As this activation did not occur in the third auditory experiment, it cannot be assigned to the modality itself but more to the complexity of the stimuli. Natural, complex visual scenes can be correctly categorised within 150ms if a denoted object category such as animals or vehicles has to be detected (Thorpe et al., 1996; Thorpe and Fabre–Thorpe, 2001; VanRullen and Thorpe, 2001). The speed of this rapid process cannot be increased with familiarity of the presented photographs but is the same for known and unknown scenes (Fabre–Thorpe et al., 2001). Complexity in vision does not seem to cause extra difficulty, but to the contrary facilitate

recognition as our system is adapted to such stimuli (Atick, 1992). A direct comparison with auditory stimuli concerning speed of processing is not applicable, because natural sounds are not presented at once such as pictures or single tones but during a certain amount of time. Compromising the OFC system with complex natural sound stimuli seemed to stress filtering/selection function of the orbitofrontal cortex.

The cause of the prominent bilateral OFC activation during the second experiment may lie in the previous presentation of the sound clips, which resulted in a familiarization and therefore a higher need already during the first run for a selection mechanism.

Auditory word repetition in general is known to activate Broca's area, Wernicke's area, posterior inferior temporal cortex, as well as left superior temporal gyrus (Price et al., 2003). We could only show similar activations in these areas, except for Broca's area that was not activated and Wernicke's area that was only activated on the right side, in the contrast first run minus third run. The first run showed also explicitly compared either with the third run or the baseline an activation in the right anterior temporal pole (BA 38) comparable to the left anterior temporal pole activation Noppeney and Price (2002) found, which was related to semantic decisions on visual and auditory presented words. During the first presentation of the 35 words the network related to auditory word processing was stronger activated than during the third presentation but not stronger than the baseline except for the temporal pole region. As the conjunction analysis revealed the first run of all auditory recognition tasks did activate the left fusiform gyrus, the same region is activated when nouns have high imageability (Wise et al., 2000) and for mental image generation (D'Esposito et al., 1997). Obviously during the first run the subjects did familiarize with the presented stimuli and generated a meaning and a mental image of it.

The comparison with the baseline did only reveal auditory related activation in the first run of the first experiment. The baseline condition seemed to activate auditory related regions with the same amount as the recognition conditions, even though only the same 3 sound clips/words were repeated over time. As different imaging studies (Buckner et al., 1995; Buckner et al., 1998; Vuilleumier et al., 2002) have shown, an adaptation and therefore a decrease in blood flow occurs due to repeated presentation at least in the visual system. The same happens with repeated presentation in the auditory cortex (Jaaskelainen et al., 2004). As the third run with the decreased activation in the auditory cortex revealed, this effect also occurred in our study but not in our baseline. It seems that the one–back task using only three different stimuli, activates the auditory cortex more than one might predict from the seeming simplicity of the task. The comparison with the baseline did only reveal auditory

related activation in the first run of the first experiment. The baseline condition seemed to activate auditory related regions with the same amount as the recognition conditions, even though only the same 3 sound clips/words were repeated over time. As different imaging studies (Buckner et al., 1995; Buckner et al., 1998; Vuilleumier et al., 2002) have shown, an adaptation and therefore a decrease in blood flow occurs due to repeated presentation at least in the visual system. The same happens with repeated presentation in the auditory cortex (Jaaskelainen et al., 2004). As the third run with the decreased activation in the auditory cortex revealed this occurred also in our study but not in our baseline. It seems as that the one–back task with only three different stimuli does activate more than predicted from the ease of the task.

Chapter 7

Memory Studies 2

In this part the continuous recognition task does not play a major role. In the first experiment the impact of the baseline task as used in the previous studies is examined. In the second experiment a new paradigm is described, which should cover the topic of a functional segregation of context and location of information in the posterior limbic system as well as the manipulation of the two information types insofar as they activate the anterior limbic system.

7.1 Effects of Baseline Task Position on Apparent Activation of Memory Critical Structures in Functional Imaging

A crucial point in functional imaging is the choice of the reference or "baseline" task. Here, we describe the influence of the temporal relation of a baseline task on apparent activations of memory critical structures during an $H_2{}^{15}O$ positron emission tomography (PET) study.

7.1.1 Introduction

Results of imaging studies of cognitive functions are strongly influenced by the choice of the baseline or control task (Raichle et al., 2001; Stark and Squire, 2001). Functional imaging methods in general have a problem insofar as in many cases relative and not absolute values are measured. Our method of measuring absolute cerebral blood flow in PET without an arterial line comprises 3 minutes of PET scanning (Treyer et al., 2003a). As it is not possible in most cognitive paradigms to hold brain activity during three minutes at the same level, measurements over one minute during the peak of measured radioactivity have to be chosen. Such measurements are relative ones as the absolute blood flow cannot be precisely

determined. Therefore a control condition i.e. a baseline, has to be introduced to define a reference.

The brain itself has no default or zero state (Mazoyer et al., 2001; Raichle et al., 2001; Stark and Squire, 2001). Therefore a baseline has to be chosen in the context of the experiment. A further problem in this context is, that cognitive functions are rarely purely additive (Friston et al., 1996; Sidtis et al., 1999). Therefore, an interpretation of the resulting subtraction "experimental task minus baseline task" is always delicate. With this study we addressed a further problem: the problem of temporal relations of memory tasks.

In our studies so far we showed that the repeated performance of a continuous recognition task leads to a different activation in the third run compared to the first run. Therefore the question arises whether or not the temporal relation between a recognition task and a similar baseline task may also be affected by a differential processing in the brain.

Our aim was to show different apparent activation of the memory task compared to the baseline task with respect to the temporal relation of them.

7.1.2 Materials and Method

The presented data were from sixteen male right–handed students aged 20 to 31 years.

Task

We used a two group design, with one group performing the baseline before (group BEFORE) and the second group after (group AFTER) the three runs of the continuous recognition task. We used the same design as in the study "subcortical loop activation during selection of currently relevant memories" (section 6.1). The data of the first block from the eight subjects, who performed the baseline after the memory task constitute the group AFTER. The eight subjects of the group BEFORE performed the baseline task before the memory task. We had therefore to counterbalance the four stimuli sets used in the previous study for the additional group BEFORE. Each set (including stimuli for memory as well as baseline task) was composed of one of four categories (meaningful line drawings (Snodgrass and Vanderwart, 1980), meaningless geometric designs, meaningful concrete nouns, pronounceable nonwords). The first run of the continuous recognition task of the to groups was used as memory task. The baseline task consisted of the repeated presentation of 2 different items of the same kind as in the memory task. The subjects had to detect immediate picture repetitions. A 6–minute break was introduced between the baseline and the continuous recognition task as

a washout period for the applied radioactivity.

Image Analysis

To reveal the effect of temporal relation of the baseline to the memory task, the group BEFORE was compared with the baseline of the group AFTER using a compare–population (AnCova) design to evaluate the between group–effects. An additional between group–effects contrast was applied on the continuous recognition task to control for possible differences between the memory activation of the two groups. To reveal an effect of the temporal relation on the subtraction "memory minus baseline" a within group analysis was performed for each group separately. We accepted significance in the a priori defined regions (orbitofrontal and mediotemporal cortex) when $p < 0.001$, uncorrected for multiple comparisons, was reached.

ROI Analysis In order to analyze the components leading to the apparent activations of memory critical structures (activity during baseline and main task), we performed a region of interest analysis on the three regions; one in the right orbitofrontal cortex and two in the left and right hippocampal formation (Figure 7.2). The regions were defined on a single slice (z=–24) with a radius of 3mm around the maximum of the activation resulting from the contrast [main Task – Baseline] of the pooled data of both groups.

7.1.3 Results

Behaviour

The tables displaying the reaction time and hit statistics are presented together with the statistical outputs in appendix A.

Overall the subjects performed well. The hit rates differed only slightly (Wilcoxon scores tested with Kruskal–Wallis method: χ^2=0, df=1, p=1) for the baseline and for the memory task (Wilcoxon scores tested with Kruskal–Wallis method: χ^2=1.16, df=1, p=0.28) between groups. The reaction times between subjects did not differ significantly for the baseline condition (median two-sample test: Z=1.7, two-sided p=0.0812) but for the memory condition (median two-sample test: Z=3.3, two-sided p=0.0009). Due to a technical problem there were missing values for one subject in the memory condition.

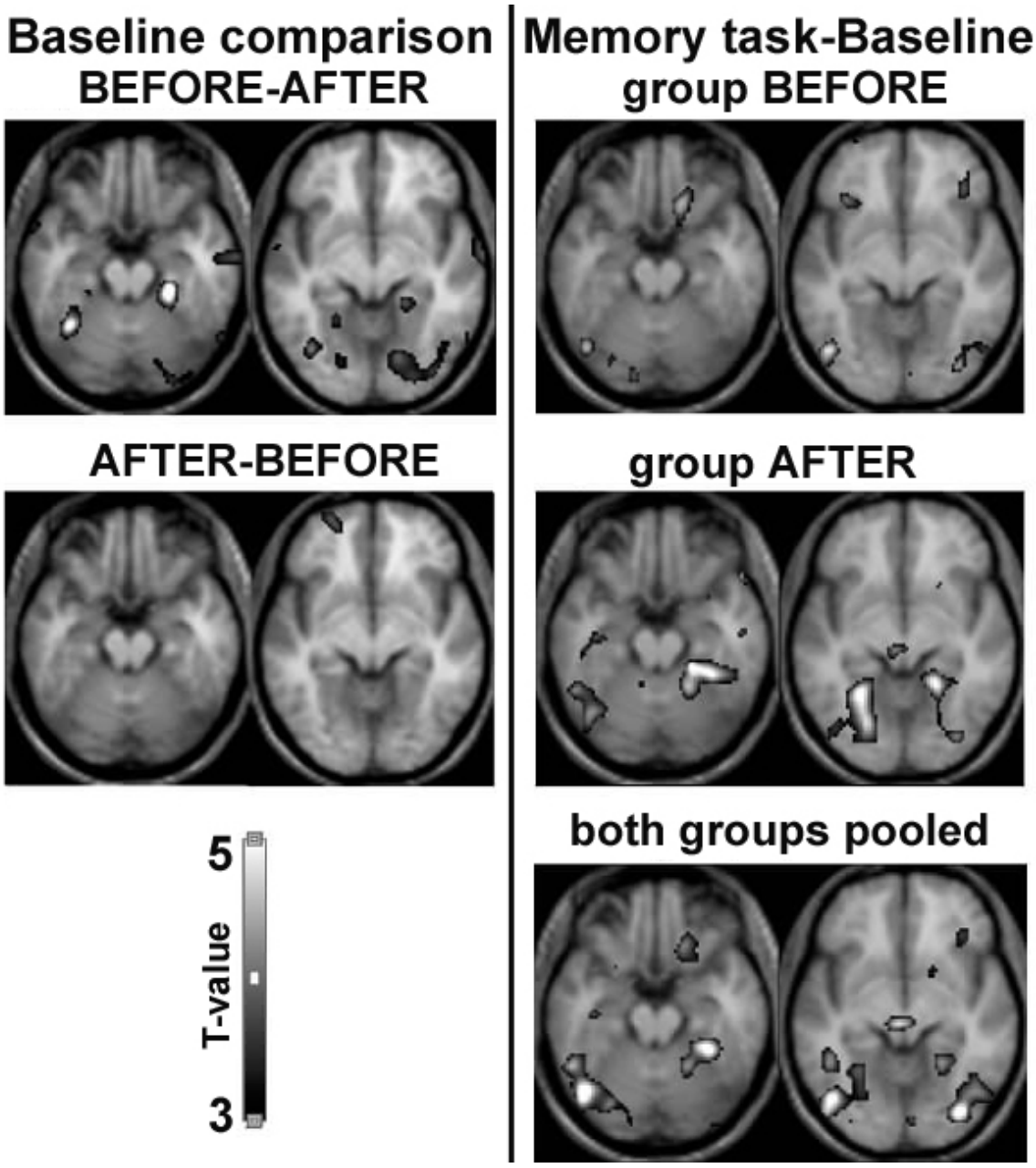

Figure 7.1: Statistical parametric maps of contrasts between task conditions displayed on two axial slices (z= –24 and –12). The left side displays direct comparison between the baseline tasks in the two groups: group BEFORE – group AFTER; group AFTER – group BEFORE. The right column of pictures shows the contrasts between the main recognition task and the baseline task in group BEFORE; group AFTER; and both groups together. The direct comparison between the main recognition tasks in the two groups did not reveal significant differences in medial temporal or orbitofrontal areas. Only significantly activated voxels are shown. SPM maps are fused with the averaged anatomical image of 8 subjects.

Cerebral Blood Flow

The results of the SPM analysis are summarized in Figure 7.1. The apparent cerebral activation during the memory task (in comparison with the respective baseline task) was different in the two groups. When the baseline task was performed first (group BEFORE), there seemed to be significantly more right orbitofrontal activation during the memory task. In the group performing the baseline task at the end (group AFTER), the recognition task appeared to induce medial temporal, and no orbitofrontal, activation. When the data of the 2 groups were pooled, both activation patterns remained significant: there were significant activations in the right orbitofrontal cortex, the right parahippocampal and the left hippocampal area. Direct comparison between the groups revealed only significantly different baseline activation but no differences between the memory tasks performed by the two groups. The baseline task performed before the recognition task induced significantly more cerebral blood flow (rCBF) in the mediotemporal region in both hemispheres than the baseline task performed after the main task (contrast: baseline in groups BEFORE – AFTER (red)). In contrast, the baseline task performed after the main task only induced significantly more activation in the left anterior orbitofrontal cortex (contrast: baseline in groups AFTER – BEFORE (green)).

ROI Analysis Figure 7.2 summarizes the ROI analysis of the 3 main areas of apparent activation in the main task obtained in the pooled data (contrast: main task – baseline). It appears that in all of these clusters, only the baseline condition induced different activation intensities; the activation during the main recognition task did not differ between the groups in any of these clusters. Thus, the presence (group AFTER, Figure 7.1b) or absence (group BEFORE, Figure 7.1a) of apparent medial temporal activation on both sides was determined by the activation during the baseline task. The results of the orbitofrontal ROI were not fully explanatory. The baseline performed by the group BEFORE seemed to less activate the right orbitofrontal cortex compared to the baseline of the group AFTER, whereas the inverse pattern seemed to be true for the main task. Both differences in the ROI analysis were not significant. Nevertheless the difference Main Task – Baseline in the group BEFORE was significant, revealing a temporal constellation in the group BEFORE which has an influence on the right orbitofrontal activation.

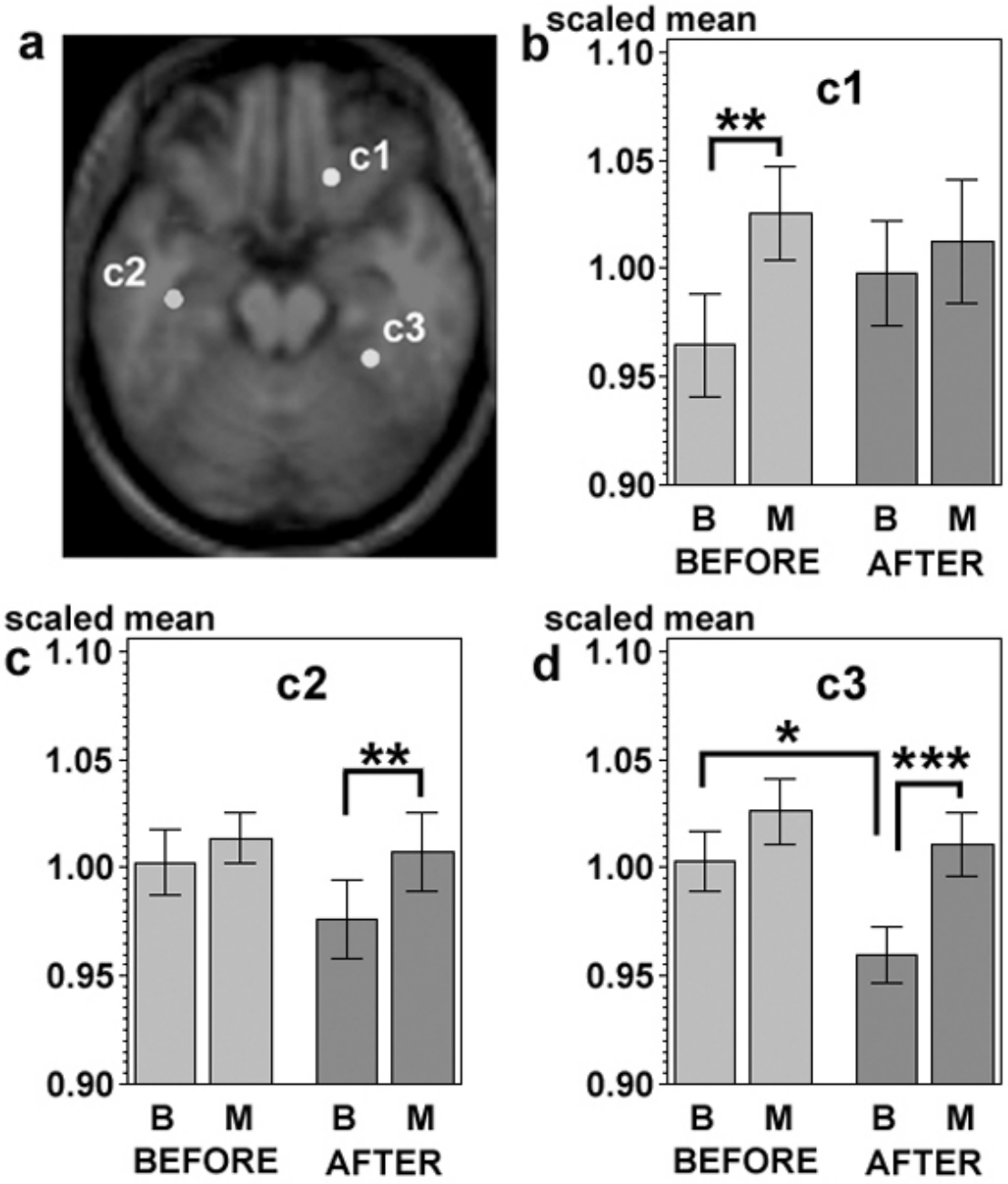

Figure 7.2: Region-of-interest analysis. a, ROIs selected from the contrast between the main recognition task - baseline in the pooled data (Figure 7.1c). b, orbitofrontal cluster c1 (2x2 ANOVA, $F(1,14) = 13.3$, $p=0.0026$; interaction Task x Group, $F(1,14) = 4.8$, $p=0.045$) with significant difference between main task (M) and baseline (B) in group BEFORE ($F(1,7)= 15.6$, $p=0.006$). c, left hippocampal cluster c2 ($F(1,14)= 12.4$, $p=0.0034$; Task x Group not significant) with significant difference between M and B in group AFTER ($F(1,7)= 13.9$; $p=0.007$). d, right parahippocampal cluster c3 ($F\ 1,14 = 27.3$, $p=0.0001$; Task x Group, $F(1,14)= 3.9$, $p=0.07$) with significant difference between M and B in group AFTER ($F(1,7)= 75$; $p < 0.0001$); in addition, significant difference between the baseline tasks ($F(1,14)= 6.2$, $p=0.026$). The y axis indicates deviations from the mean activation (1.0) of the voxels within the given cluster. Significance level: $*$ = $p < 0.05$, $**$ = $p < 0.01$, $***$ = $p < 0.001$. M = main task; B = baseline.

7.1.4 Discussion

The results showed that the relative temporal position of the baseline before or after a memory task influences the apparent activation especially of the hippocampal formation. Performing the baseline task before the memory task seemed to activate the right OFC during the memory task. But when the same baseline task was performed after the memory task, a different activation during the memory task compared with the baseline task showed up. In this group (AFTER) the hippocampal formation was activated.

This result is striking especially when considering that the between group comparison of the memory task performed either before or after the baseline task did not reveal significant activations in these regions. So we can conclude that the memory task activated the same regions in both groups. However, the brain activation during the baseline task differed between the two groups. Conducting the contrast baseline task of the group BEFORE minus baseline of the group AFTER revealed significant activation in the hippocampus formation. The different apparent activation of the contrasts memory – baseline task was due to differences between the baseline task and not the memory task. Just the fact, that an easy to perform task was made as the first task in an unfamiliar environment, activated the mediotemporal region stronger than expected.

Several possible effects could have led to these different baseline activations. One possible explanation may be that these results only reflect pure time effects as seen in other studies, which showed decreases in regional cerebral blood flow in the thalamus, the cerebellum, the frontal cortex, occipital cortex, parietal cortex and temporal cortex (Paus et al., 1997; Rajah et al., 1998) or increases in visual areas in an auditory attention task (Paus et al., 1997) and in the pre– and postcentral gyri in a visuomotor task (Rajah et al., 1998). But we reported here a dissociation of mediotemporal and frontal activation between the baselines of the two groups. A plausible explanation must comprise the new environment as well as the serial positions of conditions and not just a pure time effect.

Therefore another possible explanation is, that repeated executions of the same or a similar task in the same environment could diminish medial temporal activation (Paus et al., 1997; Rajah et al., 1998; Buchel et al., 1999). The baseline task has a small memory demand, so the medial temporal activation may reflect something different than learning and recognition related activity, but processes of familiarization with task and environment. The hippocampus is involved in the learning not only of associations between items (Henke et al., 1997; Henke et al., 1999) but also of associations of an item with the environment (Bar

and Aminoff, 2003). But can habituation to the task environment explain the different apparent activation obtained in the two groups? As the differences particularly occurred in the baseline condition, this explanation should provide an answer to the question: why was only the baseline condition affected by such familiarization effects? It is known that novelty compared to familiarity results in an increased activation of the mediotemporal cortex (Tulving et al., 1996; Stern and Hasselmo, 1999; Strange and Dolan, 2001). In this study, the baseline task consisted of two new items, but as the scan began (approx. 95s after start of the task) they were already familiar to the subjects. The first run of the continuous recognition task in contrary displayed continuously novel items together with familiar ones, in this situation higher mediotemporal activation had to be expected. One explanation may be that the novelty of the environment the task was performed in provoked this mediotemporal activation during the baseline BEFORE. An experiment on rats supports to some extent the distinction between item and environment novelty made here (Zhu et al., 1997). The authors showed that the first factor (item novelty) activated perirhinal, the second (environment novelty) hippocampal neurons. In this study, the baseline–comparison showed mediotemporal activations relatively closer to the hippocampus proper than during the continuous recognition task. The reason why the novelty of the environment did not have the same impact on the memory task may be the simplicity of the baseline task. The baseline task does not need the full amount of attention. Therefore, free capacities (as defined in (Handy, 2000)) were left to establish new but task irrelevant associations. However, when the subjects performed the baseline task afterwards, no new associations were left to be built.

Performing the baseline afterwards revealed a different pattern, i.e. a relatively higher frontal activation. It has been shown that left fronto–polar activation is related to the switching between tasks (Pollmann, 2001). But in the present study the baseline AFTER was performed 6 min after the third run of the continuous recognition task, so no immediate task switch could have occurred. The problem lies probably in the similarity of the two tasks. In both conditions, the subjects had to recognize repetitions. In the memory task repetitions were reappearances of pictures, whereas in the baseline task only immediate repetitions were the targets.

Especially in functional PET brain studies in which conditions are measured during constant stimulation of one task at a time, the problem of the temporal relation of conditions is relevant. To avoid this problem a counterbalanced design is chosen in most of the cases. But as the results of the pooled data of both groups showed, the activation reflects only the sum of the results of the within group analysis. Is the pooled apparent result more

correct than the result of the group AFTER, which only shows the relevant mediotemporal activation? If the baseline task in the group BEFORE had been tested beforehand in the scanner, the activation would probably look like that of the group AFTER as our previous studies showed.

The problem discussed here is especially prominent when a study is concerned with memory and monitoring functions. To overcome the similarity problem the baseline should be different from the experimental task but on the other hand the baseline should not be too different especially when one considers the problem that cognitive functions are rarely additive (Friston et al., 1996; Sidtis et al., 1999). To overcome the problem of the novel environment an exercise task could be performed beforehand.

This study showed the impact of the time relation of an easy to perform baseline task on to the regional cerebral blood flow pattern in healthy human subjects. Performing the baseline task as the first task, an activation of the mediotemporal regions was provoked just due to the coincidence of novel environment and free cognitive capacities. Performing the baseline after a memory task in contrary revealed a frontal activation due to the interferences from the task performed before.

The present study by itself does not allow to determine what result is more plausible, the result of the group BEFORE or AFTER. The result obtained with the baseline task performed after the memory task is more compatible with lesion data. The combined analysis, in this case, reveals activity in all areas that also appear in the separate analysis of the two groups. Nonetheless, the two versions (baseline before or after the main task) obviously measure different capacities and therefore activate different brain areas. An average of both activation patterns is hardly acceptable. We have to be aware of such most of the time unintended interactions and have to carefully select –rather than randomly distribute– baseline tasks and the moment of their presentation.

7.2 The Memory of 'What' and 'Where' and the Astonishment of not Being where Expected

7.2.1 Introduction

Ungerleider and Mishkin (1982) suggested the existence of two distinct visual pathways for the processing of content and location ("what" and "where") of visual information. Neurons in a ventral (temporofrontal) "what" pathway would code for the content of an object,

while neurons in a dorsal (parietofrontal) "where" pathway would code for the object's location. This distinction was also found in human functional imaging studies (Ungerleider and Haxby, 1994), but nevertheless not all studies support such a clear distinction as proposed. Considerable integration of these two systems can be shown (Fink et al., 1997; Sereno and Maunsell, 1998). Beside the visual system a similar segregation was reported for auditory information (Clarke et al., 1998) as well as in the dorsolateral prefrontal cortex during working memory tasks (Courtney et al., 1996).

Concerning memory functions, the hippocampal formation is particularly important for the storage and retrieval of associations between pieces of information and episodes (Henke et al., 1999; Wirth et al., 2003). Studies in rats and monkeys showed the existence of "place cells", i.e. cells that especially code spatial information, in the hippocampus proper (O'Keefe and Dostrovsky, 1971; Rolls et al., 1989). To our knowledge it is unknown, however, to what extent the segregation between "what" and "where" is maintained within the hippocampal formation.

Dissociation between left (verbal memory) and right (non–verbal and spatial memory) hippocampal formation was repeatedly demonstrated (e.g. (Burgess et al., 2002; Henke et al., 2003b)). Thus, it appears possible that the left hippocampal formation might also preferentially encode a picture's content ("what"), whereas the right hippocampal formation would encode its location in space ("where"). Even though a clear segregation of object and location based processing might not be found throughout the brain, it is feasible to confront both systems directly with each other to reveal the differences. One must, however, always keep in mind that there is an interaction going on. This interaction between the individual systems is needed to bind the features of an object together to gain the percept of an entity (Robertson, 2003).

To keep both tasks as similar as possible we did not change the presented information but asked the subjects to change their focus of attention to either a picture's content or its location. As the stimuli were in both tasks the same, a direct comparison is expected to reveal activations corresponding to the differential processing of either information.

The involvement of the hippocampus in recognition (Manns et al., 2003) and especially in the recognition of sequences of events has been shown (Fortin et al., 2002). The goal of this study was to explore the differences, rather than commonalities between the processing of content and spatial information in memory. We developed a task that demanded the recognition of deviations from a previously learned series of pictures, which were presented at specific locations. In one condition subjects had to detect deviations from the learned se-

quence's content (presentation of another picture), in the other deviation from the sequence's picture location (picture presented at another location). From the direct comparisons of the two conditions, we expected to find differential activation of the ventral and dorsal pathway as well as left and right hippocampal formation.
In addition, we used these same tasks but manipulated the non–attended information to test the ability to ignore a picture's content or location. From the studies shown in the previous chapters it is known that the orbitofrontal cortex (OFC) plays a crucial role in the suppression of certain forms of currently irrelevant memory. Therefore, we expected orbitofrontal activation during the manipulated tasks.

7.2.2 Materials and Methods

The subjects were eight right–handed male students with a mean age of 22.3±2.8 years.

Task

"What" and "Where" Conditions We explored two conditions. In both, subjects first learned a picture sequence (not scanned). Immediately afterwards the subjects had to recognize deviations from the learned sequence, this part of the experiment was scanned.
In both conditions, a sequence consisted of 6 line drawings of different objects (Snodgrass and Vanderwart, 1980), that were presented in 6 different locations out of 9 possible ones. The pictures were presented in a fixed serial order during the learning phase. Each picture was presented for three seconds at the same location (Figure 7.3). For both tasks, different picture and location sequences were chosen. The order of the tasks was counterbalanced over subjects.
In both conditions, subjects first learned the sequence in 6 consecutive runs. A run consisted of the presentation of one sequence. During the learning phase the presentation of a numbered grid for one second separated the runs. After the six learning runs, a red exclamation mark was presented for one second to indicate the start of the recognition phase. The subjects then had to press a button whenever the presented picture sequence deviated from the learned sequence in the demanded dimension, i.e. either location during the condition "where" or content during "what". Nine test runs were presented with no interruption in between. The smooth and uninterrupted presentation of the test runs should ensure that the subjects keep their attention on the serial order of the sequence during the whole time. Scanning started with the second test run.

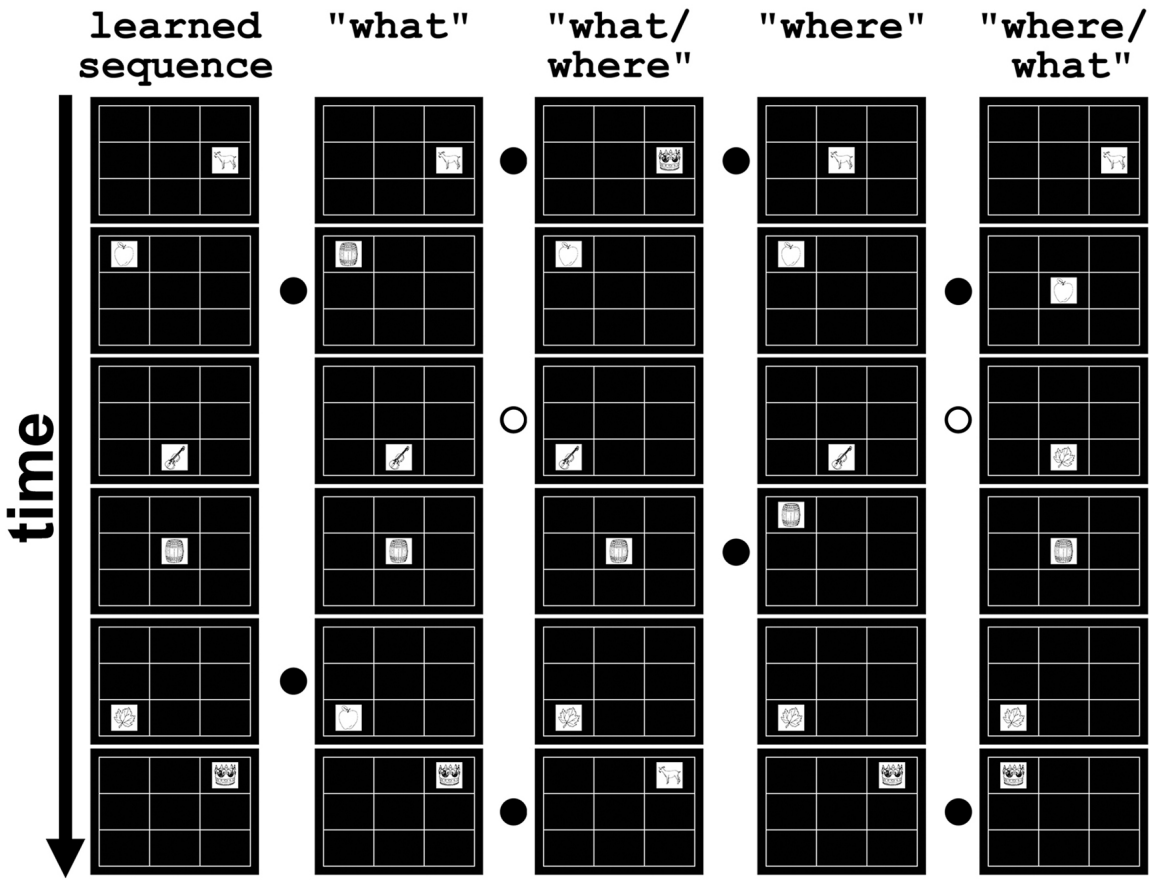

Figure 7.3: The task. The first column shows a learning sequence of six object presentations. For display purpose two objects are enlarged. The subjects received two different instructions demanding them either to learn the picture sequence's content or location. The last four columns show four test sequences. The subjects had to indicate deviations from the learned series. White circles on the left side of the grids indicate the deviations. Empty circles indicate manipulation of the non–attended information type (in the conditions "What/Where" and "Where/What"). In the PET study, each condition used different pictures and location sequences.

The subjects received instructions and a short learning and test sequence at the beginning of the experiment to familiarize them with the task. In the "what" condition the subjects had first to learn the picture sequence and had to ignore the location. The subjects were explicitly told not to pay attention to the locations neither during the learning nor the recognition phase. During recognition two pictures were changed. No new pictures were introduced. But one or two pictures were presented twice during a run. If two pictures had been just interchanged the subject would have had the opportunity to anticipate the second change.
In the "where" condition, subjects had to learn and recognize the locations in which the pictures appeared while ignoring their content. During recognition, two pictures were presented in locations deviating from the learned ones. Again no new locations were introduced.

The Manipulated Conditions ("What/Where" and "Where/What") The instruction of the condition "What/Where" was the same as for the condition "What". The two conditions differed insofar as during the recognition phase of the "What/Where" condition the location of one picture per sequence was changed. The "What/Where" condition tested the ability to ignore a task irrelevant change of location.
The instruction for the "Where/What" condition was also the same as for the "Where" condition described beforehand. During the recognition phase of the "Where/What" condition a manipulation of one picture's content per sequence was introduced in addition. Insofar as a picture's content was exchanged for another, normally appearing at another point in time within the learned sequence. The important point was that the location of appearance of this exchanged pictures remained the same. The "Where/What" condition tested the ability to ignore a task irrelevant change of picture content.

Data Analysis

As there was no "baseline" in this study direct comparisons among the four conditions were made. We accepted significance in the a priori defined regions (orbitofrontal cortex, mediotemporal lobe, temporal cortex and parietal cortex) when $p>0.001$, uncorrected for multiple comparisons.
A volume of interest (VOI) analysis was performed based on the significantly activated cluster in the mediotemporal region derived from the comparison between "What" and "Where".

7.2.3 Results

Behavioral

The subjects performed the task well: among 18 deviations, they correctly recognized 17.4±1.2 in the "What", 17.4±0.9 in the "Where", 17.8±0.5 in the "What/Where" and 17.5±0.9 in the "Where/What" condition. Only one single false alarm was produced while correct pictures or locations were presented.

The reaction times were similar, except during the "What/Where" condition, where the subjects needed more time to make their decisions. Mean reaction times±SD for correct answers were: "What", 793±233ms; "Where", 711±277ms; "What/Where", 911±291ms ; "Where/What", 718±287ms. The reaction time differences among the conditions within subjects were significant ($F(3,21)=7.62$; $p < 0.05$). A posteriori tests revealed significance only between the "What/Where" condition and all other conditions (comparison with "What": $F(1,7)=24.18$; $p < 0.01$; "Where": $F(1,7)=13.51$; $p < 0.01$; "Where/What": $F(1,7)=8.87$; $p < 0.05$).

Regional Cerebral Blood Flow

Processing of Object Information vs. Location The direct comparison between "What" and "Where" conditions revealed a significantly higher rCBF in the left hippocampal formation during "What" and in the right hippocampal formation during the "Where" condition (Figure 7.4 a). The parietal cortex as well as the right posterior medial temporal gyrus (BA 37/39) were both more activated when the subjects focused on the violation of the location rather than on the picture sequence. The left superior temporal gyrus (BA 38) and bilateral superior/medial temporal cortex (BA 22/21) were more activated during "What" than "Where". The VOI analysis of the activated left and right mediotemporal region revealed a significant interaction of condition ("What" and "Where") and side ("left" and "right") ($F(1,7)=23.81$; $p < 0.01$) (Figure 7.4 c).

Processing of Distracting Object and Location Information Comparisons between the "What/Where" and the "What" as well as between "Where/What" and "What" conditions revealed right orbitofrontal (BA 11) activation (Figure 7.4b). This contrasts revealed activation related to the manipulation. The same contrast revealed also higher activation in the right hippocampal formation as well as in the primary visual cortex (BA 17/18).

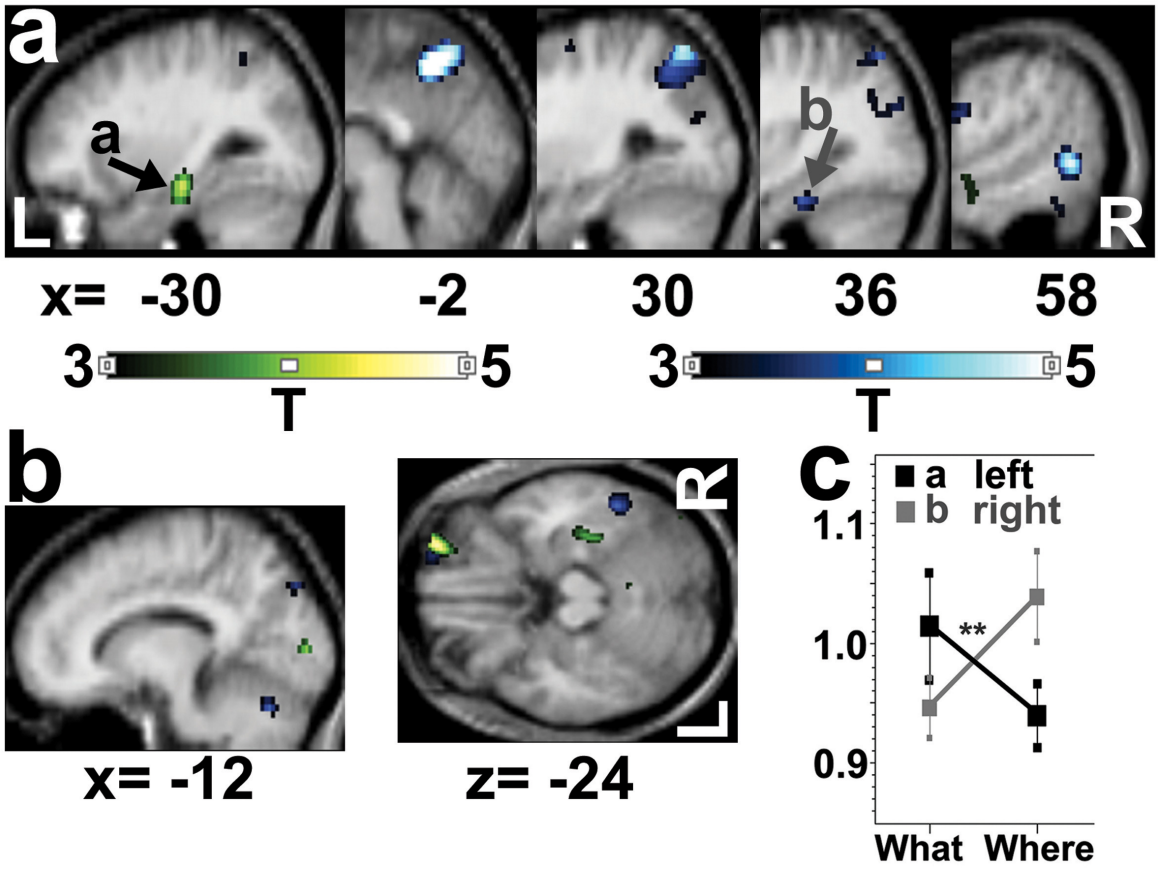

Figure 7.4: Areas of activation related to the processing of object content (a) vs. location and of distracting object and location information (b). The results are displayed with a cut–off of T=3. The statistical parametric maps are overlaid on a T1 MRI. Sagital slices are displayed from the left to the right side. MNI (Montreal Neurological Institute) coordinates are indicated on the bottom of the figure. (a) The resulting spm of the contrast "What"–"Where" is displayed in green and the results of "Where"–"What" are shown in blue. The black and grey arrow emphasis the clusters selected for the VOI– analysis. (b) The contrast "What/Where"–"What" in green and "Where/What"–"What" is displayed on a sagittal slice to show the occipital activation and on a transversal slice to present the orbitofrontal activation. (c) The VOI analysis upon the two hippocampal regions.

The comparison between "What/Where" and "Where", revealed activation in the left hippocampal formation, left superior temporal gyrus and primary visual cortex. The comparison between "Where/What" and "Where" revealed activation in the left and right superior temporal gyrus but not in the orbitofrontal cortex.

7.2.4 Discussion

What vs. Where

This study shows distinct differences of brain activation during the processing of content ("what") and location ("where") of a series of pictures. When the subjects focused on the pictures' content ("what") only, the left hippocampal formation as well as left medial temporal gyrus and bilateral superior temporal gyrus were more activated than when they concentrated on the pictures' locations ("where"). In contrast, attention to the pictures' location more strongly activated the right hippocampal formation, parietal cortex and right medial/inferior temporal gyrus than attention to the content. In both conditions, the learned sequences were similar. Thus, the differences in brain activation result specifically from the subjects detecting deviations from either the learned sequence of a picture's content ("what") or location ("where"). The activation of the right hippocampal formation is located slightly more ventral and posterior than the left activation, which suggests a more posterior and parahippocampal than hippocampal involvement during the spatial task. A recent fMRI experiment on implicit encoding of novel objects and novel spatial arrangements of familiar objects revealed also a more posterior activation of the hippocampal formation while novel spatial arrangements were presented as compared to introducing novel objects (Pihlajamaki et al., 2004). In this study both conditions were compared to a common baseline. Since we were interested in the differences, rather than commonalities, of processing content or location of objects, we used direct comparisons between the tasks rather than the comparison with a baseline task.

The hemispheric differences reported in this study are compatible with studies on material specificity (Moscovitch and McAndrews, 2002; Henke et al., 2003b): the right hippocampal formation was more activated during tasks using nonverbal information, whereas the left hippocampal formation was more involved in tasks using verbal information. In the present study, the material was the same in both conditions, namely, easily to verbalize pictures associated with a specific location.

Besides the lateralization in the hippocampal formation, there were differences in the corti-

cal activations induced by the tasks. The left superior temporal gyrus, which is involved in semantic–verbal processing (Perani et al., 1999), showed higher activation during the "what" condition than during the "where" condition. This region thus seems to be more relevant for processing a picture's content.

During the "where" condition, the parietal area BA 7, known to be important for visuo–spatial processing (Andersen, 1997), was more active. In addition, there was distinct augmentation of activity in the right posterior medial temporal gyrus (BA 37/39). This region lies close to the lateral occipital complex and is known to be involved in object recognition (Grill–Spector et al., 1999). Our result is compatible with the results of Fink et al. (2000), who found activation in the ventral system during the processing of spatial information contained in a picture, revealing an imperfect segregation of the dorsal and ventral visual pathways.

Our result indicates that inter– and intrahemispheric specialization in the processing of content and location of information markedly vary with the precise task requirements, even when the information presented in the two conditions is the same. These results reflect the direct comparison between these two conditions. Thus, these contrasts do not reveal the anatomical basis of all processes underlying the tasks, which could only be determined using a zero–baseline (Friston et al., 1996; Raichle et al., 2001; Stark and Squire, 2001). Thus, we cannot exclude that in both conditions, the hippocampal formation was bilaterally activated, but we can conclude that, dependent on the information type attended to, the left or the right side was more activated.

Manipulation of Irrelevant Information

When the subjects paid attention to the picture sequence while the location was manipulated ("What/Where"), the right OFC was activated. The comparison between "Where/What" and "What" but not the one with "Where" revealed a somewhat weaker right OFC activation. The activation in the right OFC might reflect refocusing on currently relevant information and ignoring the picture's deviant location in space. In previous PET studies we showed orbitofrontal activation during selection of relevant memory traces. These studies used a continuous recognition task. The present study also demanded adaptation of thought and action to the currently relevant – as opposed to the irrelevant – information. Nevertheless, the present study was not able to activate the OFC statistically significant in all comparisons between "What/Where" as well as "Where/What" and "What" as well "Where". But this weakness is partially consistent with the subjects' reported ease in ig-

noring mismatches in the pictures' content during the "Where/What" task.
The comparison between "What/Where" and "What" showed in addition a right mediotemporal activation. This difference may be related to the detection of the mismatch between the anticipated and the true location. It is possible that, since the subjects were asked only to learn the picture sequence, the association between the pictures and their location was only implicitly learned. Stark and Okado showed that incidental learning might activate the mediotemporal lobe (Stark and Okado, 2003). The comparison of "What/Where" and "Where" showed a left mediotemporal activation, which may relate to the higher difficulty of the manipulated condition and therefore may reflect a higher need for mediotemporal activation to solve the task. This hypothesis is in line with an fMRI study that showed the relation of successful recognition to mediotemporal activation (Daselaar et al., 2001). The exchange of pictures in the "Where/What" condition, as compared to the "Where" condition, produced additional activation in the superior temporal gyrus (BA 22 and 38). The activation in area 38 overlaps with the activation in the contrast "What"–"Where" and may therefore reflect the change of picture content which was only present in "Where/What", but not during the "Where" condition. The parietal activation (BA 7) of "Where/What" compared to "What" are also partially overlapping with the parietal activation of the contrast "Where"–"What" reflecting activation relevant to the change of picture location.
We found also a higher activation in the primary visual cortex during "What/Where". This is compatible with the significantly higher reaction time, which could reflect a requirement for extra shifts in attention and deeper inspection of the pictures. There is recent evidence that the primary visual cortex is also involved in higher visual cognition: in several electrophysiological studies in alert monkeys and also in humans studied with functional MRI, V1 activation was related to attention to targets (Posner and Gilbert, 1999). In the present study, refocusing of attention to a possible target at a different position is needed during "What/Where" and may have lead to the higher V1 activation.
In this study we were concerned about the different mnestic processing of information typically processed by the two visual pathways. We have shown that attention to information processed in the ventral pathway primarily activates the left hippocampal formation, whereas information primarily processed in the dorsal pathway activates the right hippocampal formation. Together with the activation of the two visual pathways the lateralized mediotemporal activation forms a functional neural network which can be segregated into the functions of processing picture's content or picture's location information by manipulating one or the other information type. Furthermore, we found that the right orbitofrontal cortex is involved

when task–irrelevant deviations had to be ignored. These results are in agreement with our previous imaging studies on the function of the orbitofrontal cortex.

Part IV

General Discussion and Outlook

I have already discussed my studies and linked them to the literature at the end of the each section. In this chapter instead I will focus on the links amongst the studies

Alternatives for Brain Imaging: PET vs. fMRI This thesis exclusively deals with studies that were performed using positron emission tomography (PET). For cognitive studies in healthy volunteers – besides this technique, functional magnetic resonance imaging (fMRI) has received increasing usage during recent decades. At the University of Zurich we have both, PET and fMRI, imaging tools accessible and in the course of conducting this thesis, I myself used both techniques (see my publications). Either technique has its particular advantages and disadvantages. In this section I will briefly compare both techniques and argue that PET is more suitable for the line of research described in this thesis. The arguably most prominent advantage of fMRI is that it can be used entirely non–invasively, while PET requires the injection of a radioactive substance. For PET this poses restrictions on the selection of subject groups (usually only male subjects may be used) and limits experimental time and repeatability within one individual (one experimental session per life–time). In addition, PET only allows a bad temporal resolution (in the order of minutes) as compared to fMRI (order of seconds). In turn, fMRI suffers from the disadvantage of an unpleasant, close and very noisy measurement environment. This does not only cause discomfort for the subject, but also poses limits on experimental paradigms, especially in the auditory domain. The strong magnetic field furthermore calls for technically expensive equipment, if imaging needs to be combined with any other technique. One advantage of PET is the stability of the measurements over time, as there is no phenomenon comparable to the drift of the main magnetic field that occurs in fMRI. Furthermore, as our studies concerning absolute CBF revealed, PET better measures the actual blood flow than fMRI. Most relevantly in the context of the present thesis, however, are susceptibility artefacts and geometric distortions, which come along with the fast functional imaging method. The susceptibility artefacts arise in areas, where junctions between air and tissue exist. One typical example is the brain basis (i.e. orbitofrontal cortex), where brain tissue lies close to the sinus and the inferior temporal lobe, which lies above the ear canals. Although progress in fMRI technology might improve access to the fMRI signal in these brain regions in the near future, as of now, studies in these brain regions can reliably be performed only by using PET. Nevertheless, there is one important piece of information lacking in PET: dynamic changes over short time intervals. Therefore, the paradigms used here have to induce a steady state of cognitive function and measure regional activation differences between such steady states.

Hence, we can only measure differential network activity, but cannot establish, whether a node of the network is activated after or before another one. Such a problem, however, would require a resolution on ms, which – in principle, cannot be achieved with any non–invasive technique. To answer the questions of this thesis, however, such a temporal resolution was not needed. By adequately designed paradigms, we could dissociate posterior limbic and anterior limbic function in healthy human subjects.

Reality Monitoring The main objective of this thesis was to dissociate posterior limbic and anterior limbic function in healthy human subjects. The presented studies revealed such a dissociation: the anterior limbic system is important for selection of relevant memory traces, or more precisely to filter them out of irrelevant ones. In contrast, the posterior limbic system is mainly involved in the process of encoding and retrieval of memory traces as such. Using PET, we could monitor the whole brain and reveal functional connectivity between brain regions during processing.

In our first study we showed "loop activation" and demonstrated that subcortical regions are involved in the filter function of the anterior limbic system. The activated regions are part of the dopaminergic reward system. This suggests that a modulation of this reward system will change the function of the described filtering process. Pharmacologic modulation of the subcortical dopaminergic transmission consequently offers a treatment option in spontaneous confabulating patients, who fail the task we tested in healthy volunteers. Since D2 receptors are involved in this reward system – as has been demonstrated in a computer–game–task with 11C–Raclopride as PET tracer (Koepp et al., 1998), the appropriate modulation can be achieved by a D2 receptor blocker. Following our study, Pihan et al. (2004) used this approach and demonstrated in a clinical study that a spontaneous confabulating patient, who could not perform our task before treatment, regained the required filter ability.

Performing the same task as a "matching" (targets are the repetitions) and a "non–matching" (targets are the first presentation of a stimulus) version we found that the "non–matching" version, activates strongly the basal ganglia. In contrast to our previous activation of the head of caudate together with other subcortical structures, this particular activation of basal ganglia is indeed likely to be related to motor control.

In all studies so far we found stronger cerebellum activation during both runs of the memory task as compared to the baseline task. It is known that the cerebellum is involved not only in motor related functions but also in cognition and memory. But most of the studies that focus directly on cerebellar function are related to motor skill memory or fear conditioning. Typ-

ically they are performed in rats by using foot shock–freezing behavior or airpuff–eyeblink reactions (Attwell et al., 2002; Ungerleider et al., 2002; Nitschke et al., 2004; Sacchetti et al., 2004). Most of the purely cognitive studies report cerebellum activation incidental, as did our studies (Cabeza and Nyberg, 2000; Bernard et al., 2004). A more recent study explicitly examined the involvement of the cerebellum in decision making under uncertainty (Blackwood et al., 2004). In our anticipation study presented in the introduction we also found cerebellum activation explicitly in the guessing condition compared to the baseline. In the guessing condition a decision had a probabilistic chance of 50% to be correct and therefore a higher uncertainty than in the other conditions. Also during our continuous recognition task decisions had to be taken that were, in comparison to the baseline task, more uncertain. Our studies support a relation of cerebellum functions and decision–making under certain circumstances. But it has to be tested if this relation is essential by showing that patients with lesions only in the cerebellum are impaired in this function. Further research and paradigms explicitly tailored to address these issues will be required to reveal the cerebellum's role for higher cognitive function.

Most of the memory studies in humans use visual paradigms, which is feasible as humans are best adapted to the visual world and to a lesser degree to the auditory or even olfactory domain. Nevertheless, by using auditory stimuli for our task, we could reveal the same activation pattern as for visual stimuli, even though the activations differed in strength. Auditory natural, complex stimuli, such as environmental sounds are difficult to process and need an extra amount of processing as compared to natural visual scenes. Further studies are needed to explain these results by using complex sound stimuli. One possible paradigm could include congenitally blind subjects, who are fully adapted to the auditory world and therefore should easily handle this kind of stimulation. We would predict that they show and the same dissociation with similar strength as seeing subjects that perform the same task with pictures of natural scenes.

While functional imaging is a most useful tool to study the human brain in action, the interpretation of its results is not as straightforward as is often thought. As we have exemplified in our auditory experiment the reference condition – the baseline task, itself can be a confounding factor. This especially applies to studies, in which the baseline task activates brain regions that were not expected to light up when designing the paradigm. Besides this obvious problem of "extra" activations, the timing of a task versus its baseline also requires careful consideration. We have demonstrated in our "baseline" study, the particular importance of this issue when memory function is concerned. This was also the main rationale why

I designed the "What–Where" task without an explicit baseline task. The "What–Where" task comprised two features of an object in real world, what it is (its content) and where it is (its location). Both features are closely bound together (as they are two features of one object) but also can be detached by attending only to one feature, while ignoring the other. The capability to ignore the part of the available information that is not important in the current context is a part of reality monitoring. Most of the time we are ignoring irrelevant information while focusing on for us relevant ones. By the ´What–Where´ task I intended to challenge this function. The artificial segregation of the content and location information revealed different processing in the two hemispheres. The left hippocampus was more involved in the processing of the content, while the right hippocampus preferentially processes the location information. Changing the unattended, irrelevant feature resulted in an OFC activation as predicted, especially when the changed feature is location as such a change must be noticed, processed but nevertheless ignored.

Although the results of this first study were very promising, the task needed to be adapted; it should be less artificial, but more closely mimic processing under real world conditions. In the future we will thus implement the task in a virtual environment setting. We will also transfer the continuous recognition task to such a setting. Even though the task turned out to be very fruitful, it is nevertheless an artificial task, which seems closer to a class exercise than to our every day experience. Since our processing capabilities are specifically well adapted to our natural environment it has to be tested to what extent our results transfer to real–world situations. Therefore my future experiments will address, how the brain may adapt thought and behavior of "ongoing reality" in the – at least virtual – reality.

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Lebenslauf

Name: Treyer

Vorname: Valerie

geboren am: 13. Februar 1974

Heimatort: Wölflinswil AG

Ausbildung:

1995 Kantonsschule Hottingen, Zürich ZH, Matura Typus E

1995-2000 Studium Psychologie (HF), Neurophsysiologie (1.NF) und Philosophy (2.NF) an der Universität Zürich 2000 Lizentiat in Psychologie

Titel der Lizentiatsarbeit: Neuropsychologische Leistungen vor und nach selektiver Amygdalahippocampectomie unter der Leitung von Prof. Marianne Regard

2001-2004 Promotionsstudium an der Universität Zürich

Teilnahme am Neurowissenschaftlichen PhD Kursprogramm vom Zentrum für Neurowissenschaften Zürich (Beginn 2001)

2002 Zusatzprüfung fr Fakultätswechsel bestanden (Gesuch 01–07–14)

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